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(54) FAPalpha-specific antibody with improved producibility

(57) Recombinant antibody proteins are provided that specifically bind fibroblast activation protein alpha (FAPα) and comprise framework modifications resulting in the improved producibility in host cells. The invention also relates to the use of said antibodies for diagnostic and therapeutic purposes and methods of producing said antibodies.

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Description

Field of the invention

[0001] The present invention relates to antibody proteins that specifically bind fibroblast activation protein alpha (FAPα). The invention also relates to the use of said antibodies for diagnostic and therapeutic purposes and methods of producing said antibodies.

Background of the invention

[0002] The invasive growth of epithelial cancers is associated with a number of characteristic cellular and molecular changes in the supporting stroma. A highly consistent molecular trait of the reactive stroma of many types of epithelial cancer is induction of the fibroblast activation protein alpha (from now on referred to as FAP), a cell surface molecule of reactive stromal fibroblasts originally identified with monoclonal antibody F19 (Garin-Chesa P., Old L. J. and Rettig W. J. (1990) Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. *Proc. Natl. Acad. Sci.* **87**: 7235). Since the FAP antigen is selectively expressed in the stroma of a range of epithelial carcinomas, independent of location and histological type, a FAP-targeting concept has been developed for imaging, diagnosis and treatment of epithilial cancers and certain other conditions. For this purpose a monoclonal antibody termed F19 that specifically binds to FAP was developed and described in US Patent 5,059,523, which is hereby incorporated by reference in its entirety.

[0003] One serious problem that arises when using non-human antibodies for applications *in vivo* in humans is that they quickly raise a human anti-non-human response which reduces the efficacy of the antibody in patients and impairs continued administration. Humanisation of non-human antibodies is commonly achieved in one of two ways: (1) by constructing non-human/human chimeric antibodies, wherein the non-human variable regions are joined to human constant regions (Boulianne G. L., Hozumi N. and Shulman, M .J. (1984) Production of functional chimaeric mouse/human antibody *Nature* **312**: 643) or (2) by grafting the complementarity determining regions (CDRs) from the non-human variable regions to human variable regions and then joining these "reshaped human" variable regions to human constant regions (Riechmann L., Clark M., Waldmann H. and Winter G. (1988) Reshaping human antibodies for therapy. *Nature* **332**: 323). Chimeric antibodies, although significantly better than mouse antibodies, can still elicit an anti-mouse response in humans (LoBuglio A. F., Wheeler R. H., Trang J., Haynes A., Rogers K., Harvey E. B., Sun L., Ghrayeb J. and Khazaeli M. B. (1989) Mouse/human chimeric monoclonal antibody in man: Kinetics and immune response. *Proc. Natl.* Acad. *Sci.* **86**: 4220). CDR-grafted or reshaped human antibodies contain little or no protein sequences that can be identified as being derived from mouse antibodies. Although an antibody humanised by CDR-grafting may still be able to elicit some immune reactions, such as an anti-allotype or an anti-idiotypic response, as seen even with natural human antibodies, the CDR-grafted antibody will be significantly less immunogenic than a mouse antibody thus enabling a more prolonged treatment of patients.

[0004] Another serious limitation relating to the commercial use of antibodies for diagnosis, imaging and therapy is their producibility in large amounts. In many instances recombinant expression of native, chimeric and/or CDR-grafted antibodies in cell culture systems is poor. Factors contributing to poor producibility may include the choice of leader sequences and the choice of host cells for production as well as improper folding and reduced secretion. Improper folding can lead to poor assembly of heavy and light chains or a transport incompetent conformation that forbids secretion of one or both chains. It is generally accepted, that the L-chain confers the ability of secretion of the assembled protein. In some instances multiple or even single substitutions can result in the increased producability of antibodies.

[0005] Because of the clinical importance of specific immunological targeting *in vitro* and *in vivo* of specific disease-related antigens for diagnosis and therapy in humans, there is a growing need for antibodies that combine the features of antigen specificity, low imunogenicity and high producibility.

[0006] Therefore, the problem underlying the present invention was to provide antibody proteins that combine the properties of specific binding to FAP, low immunogenicity in humans, and high producibility in recombinant systems.

Disclosure of the invention

[0007] The technical problem is solved by the embodiments characterized in the claims.

[0008] The present invention provides new antibody proteins having the complementary determining regions of the monoclonal antibody F19 (ATCC Accession No. HB 8269), said new antibody proteins specifically binding to fibroblast activation protein (FAP), characterised in that they have framework modifications resulting in the improved producability in host cells as compared to a chimeric antibody having the variable regions of F19 and foreign constant regions.

[0009] As used herein, an "antibody protein" is a protein with the antigen binding specificity of a monoclonal antibody.

[0010] "Complementarity determining regions of a monoclonal antibody" are understood to be those amino acid

sequences involved in specific antigen binding according to Kabat (Kabat E. A., Wu T. T., Perry H. M., Gottesman K. S. and Foeller C. (1991) *Sequences of Proteins of Immunological Interest* (5th Edn). NIH Publication No. 91-3242. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD.) in connection with Chothia and Lesk (Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)).

[0011] As used herein, the term "framework modifications" refers to the exchange, deletion or addition of single or multiple amino acids in the variable regions surounding the individual complementarity determining regions. Framework modifications may have an impact on the immunogenicity, producibility or binding specificity of an antibody protein.

[0012] "Fibroblast activation protein (FAP)", also designated fibroblast activation protein alpha (FAPα), is a membrane-bound glycoprotein belonging to the serine protease gene family (WO 97/34927). No shed or secreted form of FAP is known.

[0013] FAP can be characterized by its binding to the monoclonal antibody F19 (F19 is obtainable from the hybridoma cell line with the accession No. HB 8269 deposited at the ATCC).

[0014] The term „fibroblast activation protein specific binding" of an antibody protein is defined herein by its ability to specifically recognise and stably bind FAP-expressing human cells. The binding specificity of the proteins of the invention can be determined by standard methods for the evaluation of binding specificity such as described in an exemplary fashion in example 6, 8 and example 12.

[0015] The term „chimeric antibody" refers to an antibody protein having the light and heavy chain variable regions as described in figures 17 and 18 and foreign constant regions. „Foreign constant regions" as defined herein are constant regions which are different from the constant regions of F19. For comparing an antibody protein of the invention to a chimeric antibody it is to be understood that such a chimeric antibody must contain the same constant regions as said antibody protein. For the purpose of demonstration and comparison alone the human constant heavy and light chains as described in Figures 19 to 22 are used in an exemplary fashion.

[0016] To provide the antibody proteins of the present invention, the nucleic acid sequences of the heavy and light chain genes of the murine antibody designated F19 were determined from RNA extracted from F19 hybridoma cells (ATCC Accession No. HB 8269).

[0017] In one embodiment the present invention relates to antibody proteins having the complementary determining regions of the monoclonal antibody F19 (ATCC Accession No. HB 8269), said new antibody proteins specifically binding to fibroblast activation protein (FAP), characterized in that they have framework modifications resulting in the improved producability in host cells as compared to a chimeric antibody having the variable regions of F19 and foreign constant regions, wherein said antibody protein is derived from the murine antibody designated F19 (ATCC Accession No. HB 8269).

[0018] To generate humanised FAP-specific antibody proteins a chimeric antibody was constructed, having variable regions of the light and heavy chains of F19 and human light and heavy constant regions, respectively. The construction and production of chimeric mouse/human antibodies is well known (Boulianne et al. (1984), referenced above) and demonstrated in an exemplary fashion in examples 1 and 2.

[0019] Therefore, in a further embodiment the invention relates to antibody proteins according to the invention, characterised in that they have a variable light chain region and a variable heavy chain region, each joined to a human constant region.

[0020] In particular, the variable region of the light chain was joined to a human kappa constant region and the variable region of the heavy chain was joined to a human gamma-1 constant region. Other human constant regions for humanising light and heavy chains are also available to the expert. A human kappa and a human gamma-1 constant regions were used for demonstrating the invention in an exemplary fashion only.

[0021] Therefore, in one particular embodiment the antibody proteins of the invention contain a human kappa constant region.

[0022] Also, in another particular embodiment the antibody proteins of the invention contain a human gamma-1 constant region.

[0023] One particular „chimeric F19 antibody" protein (cF19) consists of the light and heavy chain variable and constant regions described in Figures 17 to 22. cF19 demonstrates specific binding and high avidity to the FAP antigen. As demonstrated in example 2, the expression of cF19 in COS cells is poor, ranging from about 10 to 60 ng/ml, which is at least 10 fold less than most antibodies.

[0024] In an attempt to increase expression levels of cF19, the leader sequence of the F19 V_L region was changed by substitution of Proline to Leucine at position -9.

[0025] This single change in amino acid in the leader sequence resulted in at least doubling the amount of chimeric antibody produced in COS cells. For the expression of this particular chimeric antibody in COS cells the following mutated leader sequence of the light chain: MDSQAQVLMLLLLWVSGTCG, and the following leader sequence of the heavy chain: MGWSWVFLFLLSGTAGVLS were used.

[0026] According to the invention the term "improved producibility" in host cells refers to the substantial improvement of expression levels and/or purified antibody yields when compared with the expression levels and/or antibody yields of

a chimeric antibody without framework modifications as defined above. Two particular but not limiting examples for demonstrating improved producibility are exemplified for the COS cell expression system (in examples 2 and 5) and for the CHO cell expression system (in example 10 and 11).

[0027] While the mutation of the leader sequence only lead to the doubling of the expression yield of the chimeric F19 antibody, a substantial improvement as defined herein refers to an improvement in expression level and/or purification yield of at least a factor of 10.

[0028] In a preferred embodiment, the invention refers to antibody proteins, characterised in that their expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 10.

[0029] In more preferred embodiment, the invention refers to antibody proteins, characterised in that their expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 20.

[0030] In a most preferred embodiment, antibody proteins, characterised in that their expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 100.

[0031] Improved producability of the recombinant antibody proteins of the invention can be demonstrated for eucaryotic cells in general as shown for COS (cells derived from the kidney of an African green monkey) and CHO (Chinese hamster ovary derived cells) eucaryotic cells (see examples 5 and 11). In a further embodiment, the present invention relates to recombinant antibody proteins characterised in that they display improved producability in eucaryotic cells.

[0032] In a preferred embodiment the present invention relates to antibody proteins, wherein said eucaryotic cell is a chinese hamster ovary cell (CHO cell).

[0033] It was unexpectably found that certain framework modifications of the light chain variable regions determine the improved producibility of the antibody proteins of the invention. Three versions of reshaped light chain variable regions, designated version A, B, and C, as described in Figures 1 to 6, were prepared.

[0034] Light chain variable region versions A, B, and C demonstrate substantially improved producibility in CHO cells (see example 11). While light chain variable region versions A and C differ from light chain variable region version B by only two common amino acid residues they display an even further substantial improvement in producibility. There is at least another 10 fold difference in antibody secretion levels between the human reshaped F19 light chain version B and versions A or C. Reshaped human F19 light chain version A and B only differ in their amino acid sequences by two residues at positions 36 (Tyr to Phe mutation) and 87 (Tyr to Asp mutation) (nomenclature according to Kabat). This negative effect on the secretory capability of antibodies containing the light chain variable region version B could have been indirect if the Tyr to Asp and Tyr to Phe mutations, considered individually or together, merely caused improper folding of the protein. But this is unlikely to be the case since antigen binding assays show that immunoglobulins containing F19 light chain version B have similar avidities to those paired with F19 light chain version A or C, suggesting that they were not grossly misfolded.

[0035] Residue 87 in reshaped human F19 light chain version B seems particularly responsible for the reduction of secretion when compared to versions A and C.

[0036] In a preferred embodiment, the present invention relates to antibody proteins according to the invention, wherein the amino acid in Kabat position 87 of the light chain region is not asparagine.

[0037] In a more preferred embodiment, the invention relates to antibody proteins according to the invention, wherein the amino acid in Kabat position 87 of the light chain region is selected from aromatic or aliphatic amino acids.

[0038] In a most preferred embodiment, the present invention relates to antibody proteins according to the invention, wherein the aromatic amino acid in Kabat position 87 of the light chain region is a tyrosine or phenylalanine.

[0039] In a further embodiment, the present invention also pertains to antibody proteins according to the invention, wherein the aminoacid in Kabat position 36 of the light chain region is selected from aromatic amino acids.

[0040] In a particular embodiment the invention relates to the specific antibody proteins that may be prepared from the individually disclosed reshaped variable regions of the light and heavy chains.

[0041] Especially light chain variable region versions A and C are particularly suitable to practice the invention because of their exceptionally high producability, while retaining full FAP-binding specificity and achieving low immunogenicity. This holds especially true when compared to the chimeric antibody having the variable regions of F19 and the same constant regions but also when compared to light chain version B.

[0042] Therefore, in one embodiment the present invention relates to antibody proteins that contain the variable region of the light chain as set forth in SEQ ID NO: 2. In a further embodiment the invention also relates to antibody proteins, characterised in that the variable region of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1.

[0043] In one embodiment the present invention relates to antibody proteins that contain the variable region of the light chain as set forth in SEQ ID NO: 6.

[0044] In a further embodiment the invention also relates to antibody proteins characterised in that the variable region

of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 5.

[0045] The present invention also discloses several different variable regions of the heavy chain that work particularly well with the variable regions of the light chain versions A and C in terms of improved producability.

[0046] In one embodiment the invention relates to antibody proteins containing a variable region of the heavy chain as set forth in any one of SEQ ID NOs: 8, 10, 12, 14.

[0047] In another embodiment the invention relates to antibody proteins characterised in that the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in any one of SEQ ID NOs: 7, 9, 11, 13.

[0048] In a very particular embodiment the invention relates to antibody proteins containing the variable region of the light chain as set forth in SEQ ID NO: 2 and the variable region of the heavy chain as set forth in SEQ ID NOs: 12.

[0049] In a further particular embodiment the invention relates to antibody proteins characterised in that the variable region of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1 and the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 11.

[0050] In a further particular embodiment the invention relates to antibody proteins containing the variable region of the light chain as set forth in SEQ ID NO: 2 and the variable region of the heavy chain as set forth in SEQ ID NOs: 8.

[0051] In a further particular embodiment the invention relates to antibody proteins characterised in that the variable region of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1 and the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 7.

[0052] In a further aspect, the present invention relates to nucleic acid molecules containing the coding information for the antibody proteins according to the invention as disclosed above. Preferably, a nucleic acid molecule according to the present invention is a nucleic acid molecule containing a nucleotide sequence selected from SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, or 15.

[0053] A further aspect of the present invention is a recombinant DNA vector containing the nucleotide sequence of any one of the above-mentioned nucleic acids, especially when said nucleotide sequence is operationally linked to an expression control sequence as in expression vectors. Preferred is a recombinant DNA vector, said vector being an expression vector.

[0054] A further aspect of the present invention is a host cell carrying a vector as described, especially an expression vector. Such a host cell can be a procaryotic or eucaryotic cell. Preferably, such a host cell is a eucaryotic cell, a yeast cell, or a mammalian cell. More preferably, said host cell is an CHO (Chinese hamster ovary) cell or a COS cell.

[0055] Accordingly, a still further aspect of the present invention is a method of producing antibody proteins according to the invention. Such a method comprises the steps of:

(a) cultivating a host cell as described above under conditions where said antibody protein is expressed by said host cell, and
(b) isolating said antibody protein.

[0056] Mammalian host cells, preferably CHO or COS cells are preferred. Host cells for producing the antibody proteins of the invention may be transfected with a single vector containing the expression units for both, the light and the heavy chain. In one particular embodiment the method of producing antibody proteins according to the invention pertains to host cells, wherein said host cells are cotransfected with two plasmids carrying the expression units for the light and heavy chains respectively.

[0057] The antibody proteins of the invention provide a highly specific tool for targeting therapeutic agents to the FAP antigen. Therefore, in a further aspect, the invention relates to antibody proteins according to the invention, wherein said antibody protein is conjugated to a therapeutic agent. Of the many therapeutic agents known in the art, therapeutic agents selected from the group consisting of radioisotopes, toxins, toxoids, inflammatogenic agents, enzymes, antisense molecules, peptides, cytokines, and chemotherapeutic agents are preferred.

[0058] Among the radioisotopes gamma, beta and alpha-emitting radioisotypes may be used as a therapeutic agent. β-emitting radioisotopes are preferred as therapeutic radioisotopes. ^{186}Rhenium, ^{188}Rhenium, ^{131}Iodine and ^{90}Yttrium have been proven to be particularly useful β-emitting isotopes to achieve localized irradiation and destruction of malignant tumor cells. Therefore, radioisotopes selected from the group consisting of ^{186}Rhenium, ^{188}Rhenium, ^{131}Iodine and ^{90}Yttrium are particularly preferred as therapeutic agents conjugated to the antibody proteins of the invention.

[0059] A further aspect of the present invention pertains to antibody proteins according to the invention, characterised in that they are labeled. Such an FAP-specific labeled antibody allows for the localisation and/or detection of the FAP antigen *in vitro* and/or *in vivo*. A label is defined as a marker that may be directly or indirectly detectable. An indirect marker is defined as a marker that cannot be detected by itself but needs a further directly detectable marker specific for the indirect marker. Preferred labels for practicing the invention are detectable markers. From the large variety of detectable markers, a detectable marker selected from the group consisting of enzymes, dyes, radioisotopes, and biotin is most preferred.

[0060] A further aspect of the present invention relates to antibody proteins according to the invention, characterised

in that they are conjugated to an imageable agent. A large variety of imageable agents, especially radioisotopes, are available from the state o the art. For practicing the invention gamma-emitting isotopes are more preferred. Most preferred is ^{125}Iodine.

[0061] One aspect of the present invention relates to pharmaceutical compositions containing an antibody protein according to the present invention as described above and a pharmaceutically acceptable carrier useful for treating tumors, wherein said tumors are associated with activated stromal fibroblasts. There are two possible effector principles for an anti-tumor stroma immunotherapy that may act synergistically: (a) An unmodified (unconjugated, 'naked') antibody according to the invention may induce immune destruction or inflammatory reactions in the tumor stroma while (b) an antibody conjugated to a therapeutic agent, such as for example, a radioisotope or other toxic substance, may achieve localized irradiation and destruction of the malignant tumor cells.

[0062] One further embodiment are pharmaceutical compositions containing an antibody protein according to the invention conjugated to a therapeutic agent as described above and a pharmaceutically acceptable carrier useful for treating tumors, wherein said tumors are associated with activated stromal fibroblasts. Another embodiment pertains to pharmaceutical compositions containing an antibody protein according to the present invention conjugated to an imageable agent as described above and a pharmaceutically acceptable carrier useful for imaging the presence of activated stromal fibroblasts in a healing wound, inflamed skin or a tumor, in a human patient. A most preferred embodiment relates to the pharmaceutical compositions mentioned above, wherein said tumors are tumors selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, invasive bladder cancers, pancreatic cancers and cancers metastatic of the brain.

[0063] In an animal or human body, it can proove advantageous to apply the pharmaceutical compositions as described above via an intravenous or other route, e.g. systemically, locally or topically to the tissue or organ of interest, depending on the type and origin of the disease or problem treated, e.g. a tumor. For example, a systemic mode of action is desired when different organs or organ systems are in need of treatment as in e.g. systemic autoimmune diseases, or allergies, or transplantations of foreign organs or tissues, or tumors that are diffuse or difficult to localise. A local mode of action would be considered when only local manifestations of neoplastic or immunologic action are expected, such as, for example local tumors.

[0064] The antibody proteins of the present invention may be applied by different routes of application known to the expert, notably intravenous injection or direkt injektion into target tissues. For systemic application, the intravenous, intravascular, intramuscular, intraarterial, intraperitoneal, oral, or intrathecal route are preferred.

[0065] A more local application can be effected subcutaneously, intracutaneously, intracardially, intralobally, intramedullarly, intrapulmonarily or directly in or near the tissue to be treated (connective-, bone-, muscle-, nerve-, epithilial tissue). Depending on the desired duration and effectiveness of the treatment, pharmaceutical antibody compositions may be administered once or several times, also intermittently, for instance on a daily basis for several days, weeks or months and in different dosages.

[0066] For preparing suitable antibody preparations for the applications described above, the expert may use known injectable, physiologically acceptable sterile solutions. For preparing a ready-to-use solution for parenteral injection or infusion, aqueous isotonic solutions, such as e.g. saline or corresponding plasmaprotein solutions are readily available. The pharmaceutical compositions may be present as lyophylisates or dry preparations, which can be reconstituted with a known injectable solution directly before use under sterile conditions, e.g. as a kit of parts. The final preparation of the antibody compositions of the present invention are prepared for injection, infusion or perfusion by mixing purified antibodies according to the invention with a sterile physiologically acceptable solution, that may be supplemented with known carrier substances or/and additives (e.g. serum albumine, dextrose, sodium bisulfite, EDTA).

[0067] The amount of the antibody applied depends on the nature of the disease.

[0068] Furthermore, one aspect of the present invention relates to the use of the antibody proteins according to the invention for the treatment of cancer. In a preferred embodiment the present invention relates to the use of antibody proteins according to the invention conjugated to a therapeutic agent as described above for the treatment of cancer. In another preferred embodiment the present invention relates to the use of antibody proteins according to the invention conjugated to an imageable agent for imaging activated stromal fibroblasts. In a further preferred embodiment the present invention relates to the use of labeled antibody proteins according to the invention for detecting the presence of activated stromal fibroblasts in a sample.

[0069] One aspect of the invention relates to a method of treating tumors, wherein the tumor is associated with activated stromal fibroblasts capable of specifically forming a complex with antibody proteins according to the invention, present as naked/unmodified antibodies, modified antibody proteins, such as e.g. fusion proteins, or antibody proteins conjugated to a therapeutic agent, which comprises contacting the tumor with an effective amount of said antibodies. In a preferred embodiment the present invention relates to a method of treating tumors as mentioned above, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, invasive bladder cancers, pancreatic cancers and metastatic cancers of the brain. The method of treating tumors as described above my be effected in

in vitro or *in vivo*.

[0070] A further aspect of the invention relates to a method of detecting the presence of activated stromal fibroblasts in wound healing, inflammation or in tumors, characterised in that

(a) a sample, possibly containing activated stromal fibroblasts, is contacted with an antibody protein according to the invention under conditions suitable for the formation of a complex between said antibody and antigen,
(b) detecting the presence of said complex, thereby detecting the presence of activated stromal fibroblasts in wound healing, inflammation or a tumor.

[0071] In a preferred embodiment, the present invention relates to a method of detecting the presence of activated stromal fibroblasts in a tumor, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain. Most preferred antibody proteins of the invention are those which are characterised in that they are labeled as mentioned above.

[0072] A further aspect of the invention relates to a method of imaging the presence of activated stromal fibroblasts in a healing wound, inflamed skin or a tumor, in a human patient, characterised in that

(a) an antibody protein according to the present invention conjugated to an imageable agent is administered to a human patient under conditions suitable for the formation of an antibody-antigen complex,
(b) imaging any complex formed in this manner,
(c) thereby imaging the presence of activated stromal fibroblasts in a human patient.

[0073] In a preferred embodiment the present invention relates to a method of imaging the presence of activated stromal fibroblasts as described above in tumors, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain.

[0074] In a further aspect the present invention relates to a method of detecting tumor-stroma, characterised in that

(a) a suitable sample is contacted with an antibody protein according to the present invention, under conditions suitable for the formation of an antibody-antigen complex,
(b) detecting the presence of any complex so formed,
(c) relating the presence of said complex to the presence of tumor-stroma.

[0075] Antibody proteins for practicing the invention are preferably labelled with a detectable marker.

[0076] In a further aspect the present invention relates to a method of imaging tumor-stroma in a human patient, which comprises

(a) adminstering to the patient an antibody according to the invention conjugated to an imageable agent as described above under conditions suitable for the formation of an antibody-antigen complex,
(b) imaging any complex so formed, and thereby imaging the presence of tumor-stroma in a human patient.

Figure legends

[0077]

Fig. 1. *DNA sequence of F19 human reshaped light chain variable region version A (hF19L$_A$) SEQ ID NO:1.*

Fig. 2. *Amino acid sequence of F19 human reshaped light chain variable region version A (hF19L$_A$) SEQ ID NO: 2.*

Fig. 3. *DNA sequence of F19 human reshaped light chain variable region version B (hF19L$_B$) SEQ ID NO: 3.* Nucleotides differing from version A are underlined and in bold type.

Fig. 4. *Amino acid sequence of F19 human reshaped light chain variable region version B (hF19L$_B$) SEQ ID NO: 4.* Amino acids differing from version A are underlined and in bold type.

Fig. 5. *DNA sequence of F19 human reshaped light chain variable region version C (hF19L$_C$) SEQ ID NO:5.* Nucleotides differing from version A are underlined and in bold type.

Fig. 6. *Amino acid sequence of F19 human reshaped light chain variable region version C ($hF19L_C$) SEQ ID NO: 6.* Amino acids differing from version A are underlined and in bold type.

Fig. 7. *DNA sequence of F19 human reshaped variable region heavy chain version A ($hF19H_A$) SEQ ID NO: 7.*

Fig. 8. *Amino acid sequence of F19 human reshaped heavy chain variable region version A ($hF19H_A$) SEQ ID NO: 8*

Fig. 9. *DNA sequence of F19 human reshaped heavy chain variable region version B ($hF19H_B$) SEQ ID NO: 9.* Nucleotides differing from version A are underlined and in bold type.

Fig. 10. *Amino acid sequence of F19 human reshaped heavy chain variable region version B ($hF19H_B$) SEQ ID NO: 10.* Amino acids differing from version A are underlined and in bold type.

Fig. 11. *DNA sequence of F19 human reshaped heavy chain variable region version C ($hF19H_C$) SEQ ID NO: 11.* Nucleotides differing from version A are underlined and in bold type.

Fig. 12. *Amino acid sequence of F19 human reshaped heavy chain variable region version C ($hF19H_C$) SEQ ID NO: 12.* Amino acids differing from version A are underlined and in bold type.

Fig. 13. *DNA sequence of F19 human reshaped heavy chain variable region version D ($hF19H_D$) SEQ ID NO: 13.* Nucleotides differing from version A are underlined and in bold type.

Fig. 14. *Amino acid sequence of F19 human reshaped heavy chain variable region version D ($hF19H_D$) SEQ ID NO: 14.* Amino acids differing from version A are underlined and in bold type.

Fig. 15. *DNA sequence of F19 human reshaped heavy chain variable region version E ($hF19H_E$) SEQ ID NO: 15.* Nucleotides differing from version A are underlined and in bold type.

Fig. 16. *Amino acid sequence of F19 human reshaped heavy chain variable region version E ($hF19H_E$) SEQ ID NO: 16.* Amino acids differing from version A are underlined and in bold type

Fig. 17. *Amino acid sequence of F19 chimeric light chain variable region (chF19LC) SEQ ID NO: 17.*

Fig. 18. *Amino acid sequence of F19 chimeric heavy chain variable region (chF19HC) SEQ ID NO: 18.*

Fig. 19. *DNA sequence of human kappa light constant chain SEQ ID NO: 19.*

Fig. 20. *Amino acid sequence of human light constant chain SEQ ID NO: 20.*

Fig. 21. *DNA sequence of human heavy constant chain SEQ ID NO: 21.*

Fig. 22. *Amino acid sequence of human heavy constant chain SEQ ID NO: 22.*

Fig. 23. *Mammalian cell expression vectors used to produce chimeric and reshaped human antibodies with human kappa light chains and human gamma-1 heavy chains.*

A. Light chain expression vector: pKN100
B. Heavy chain expression vector: pG1D105

Fig 24. *DNA and amino acid sequences of mouse F19 light chain variable region as modified for use in the construction of chimeric F19 light chain.* Restriction sites are indicated by bold letters. The Kozak sequence, CDR's 1 to 3 and the splice donor site are underlined.

Fig 25. *DNA and amino acid sequences of mouse F19 heavy chain variable region as modified for use in the construction of chimeric F19 heavy chain.* Restriction sites are indicated by bold letters. The Kozak sequence and the splice donor site are underlined.

Fig. 26. *DNA sequence of F19 chimeric antibody cloned into pKN100 mammalian expression vector.* Restriction sites are indicated by bold letters and underlined. CDR's 1 to 3 and the splice donor site are underlined. This is the DNA sequence of the mouse F19 light chain inside the pKN100 eukaryotic expression vector. This vector has a cDNA version of the human kappa constant region gene (allotype Km(3)) terminated by a strong artificial termination sequence. In addition, the Neo selection gene is also terminated by this artificial sequence and is also in the same orientation as the kappa light chain expression cassette.

The essential components of the pKN100 eukaryotic expression vector are:

1 - 6	= EcoRI site
7 - 1571	= HCMVi promoter/enhancer
583 - 587	= TATAA box
610	= Start of transcription
728 - 736	= Splice donor site
731	= Beginning of intron
1557	= End of intron
1544 - 1558	= Splice acceptor site
1590 - 1598	= Kozak sequence
1599 - 1658	= peptide leader sequence
1659 - 1997	= mouse F19 light chain
1996 - 2004	= splice donor site
2011 - 2657	= cDNA copy of human Kappa constant region (Km(3)) gene
2664 - 2880	= Artificial spaC2 termination sequence
2887 - 7845	= This is the pSV2neo vector DNA fragment comprising of the Amp-resistance gene (in the opposite orientation), the ColEI and SV40 origins of replication and the Neo-resistance gene (in the same orientation as the HCMVi-KCT cassette)
7852 - 8068	= Artificial spaC2 termination signal

This sequence ends immediately upstream of the EcoRI site (position 1-6) at the beginning of the sequence. As a vector this DNA sequence would be circular.

Fig. 27. *DNA sequence of F19 chimeric antibody cloned into pg1d105 mammalian expression vector.* Restriction sites are indicated by bold letters and underlined. CDR's 1 to 3 and the splice donor site are underlined. This is the DNA sequence of the eukaryotic expression vector pG1D105 containing the mouse F19 heavy chain variable region. This vector contains a cDNA version of the human gamma-1 constant region (allotype $G1m^{Non-a}$).

The essential components of the construct are:

1 - 2501	= pBR322 based sequence including Ampicillin resistance gene and ColEI origin plus the SV40 origin and the crippled SV40 early promoter
2502 - 3226	= dhfr gene
3233 - 4073	= SV40 poly A sequence etc.
4074 - 4079	= ligated BamHI and BglII site (BstYI)
4080 - 4302	= SPA site plus C2 termination signal
4303 - 5867	= HCMVi promoter
5879 - 5885	= unique HindIII restriction site for cloning of immunoglobulin variable genes
5886 - 5894	= Kozak sequence
5895 - 5951	= signal peptide
5952 - 6323	= mouse F19 heavy chain
6323 - 6330	= splice donor site
6331 - 6336	= unique BamHI restriction site for cloning of immunoglobulin variable genes
6337 - 7388	= cDNA copy of human gamma-1 constant regions preceded by a 62 bp intron
7389 - 7709	= Arnie termination sequence

The human gamma-1 constant region used in this construct has a $G1m^{Non-a}$ allotype which is defined by a Glutamic acid (E) residue at position 356 (according to Eu numbering) and a Methionine (M) residue at position 358 (according to Eu numbering). These two residues are underlined in the sequence above.

Fig. 28. *PCR-based method for the construction of human reshaped F19 light chain.* This figure provides a schematic overview of the strategy of construction. The dotted lines indicate a complementary sequence of at least 21

bases between the primers.

Fig. 29. *Nucleotide and deduced amino acid sequences of reshaped human F19 light chain variable regions version A, B and C.* Nucleotide and deduced amino acid sequences are aligned and compared with that of version A, dashes indicate nucleotide identity, dots indicate amino acid identity with this sequence. Amino acids are numbered according to Kabat *et al.* (1991). The locations of CDRs are indicated in boxes.

Fig. 30. *DNA sequence of F19 L_A (human reshaped light chain version A) cloned into pKN100 mammalian expression vector.* Restriction sites are indicated by bold letters and underlined. CDR's 1 to 3 and the splice donor site are underlined. This is the DNA sequence of the reshaped F19 light chain version A cloned into pKN100 eukaryotic expression vector. This vector has a cDNA version of the human kappa constant region gene (allotype Km(3)) terminated by a strong artificial termination sequence. In addition, the Neo selection gene is also terminated by this artificial sequence and is also in the same orientation as the kappa light chain expression cassette.

The components of the vector are:

7 - 1571	= HCMVi promoter/enhancer
583 - 587	= TATAA box.
610	= Start of transcription.
728 - 736	= Splice donor site.
731	= Beginning of intron.
1557	= End of intron.
1544 - 1558	= Splice acceptor site.
1590 - 1598	= Kozak sequence
1599 - 1658	= peptide leader sequence
1659 - 1997	= reshaped F19 light chain version A
1996 - 2004	= splice donor site
2011 - 2657	= cDNA copy of human kappa constant region (Km(3)) gene.
2664 - 2880	= Artificial spaC2 termination sequence.
2887 - 7845	= This is the pSV2neo vector DNA fragment comprising of the Amp-resistance gene (in the opposite orientation), the ColEI and SV40 origins of replication and the Neo-resistance gene (in the same orientation as the HCMVi-KCT cassette).
7852 - 8068	= Artificial spaC2 termination signal.

This sequence ends immediately upstream of the EcoRI site (position 1-6) at the beginning of the sequence below. As a vector this DNA sequence would be circular.

Fig. 31. *PCR-based method for the construction of human reshaped F19 heavy chain.* This figure provides a schematic overview of the strategy of construction. The dotted lines indicate a complementary sequence of at least 21 bases between the primers.

Fig. 32. *Nucleotide and deduced amino acid sequences of reshaped human F19 heavy chain variable region versions a to e.* Nucleotide and deduced amino acid sequences are aligned and compared with that of version A, dashes indicate nucleotide identity, dots indicate amino acid identity with this sequence. Amino acids are numbered according to Kabat *et al.* (1991). The location of CDRs is indicated by boxes.

Fig. 33. *DNA sequence of F19Ha (human reshaped heavy chain version a) cloned into pg1d105 mammalian expression vector.* Restriction sites are indicated by bold letters and underlined. CDR's 1 to 3 and the splice donor site are underlined. This is the DNA sequence of the eukaryotic expression vector pG1D105 containing the reshaped version A of F19 heavy chain variable region. This vector contains a cDNA version of the human gamma-1 constant region (allotype $G1m^{Non-a}$).

The essential components of the construct are:

1 - 2501	= pBR322 based sequence including Ampicillin resistance gene and ColEI origin plus the SV40 origin and the crippled SV40 early promoter
2502 - 3226	= dhfr gene
3233 - 4073	= SV40 poly A sequence etc.
4080 - 4302	= SPA site plus C2 termination signal
4303 - 5867	= HCMVi promoter/enhancer

5879 - 5885 = unique HindIII restriction site for cloning of immunoglobulin variable genes
5886 - 5894 = Kozak sequence
5895 - 5951 = signal peptide
5952 - 6323 = reshaped F19 heavy chain version A
6323 - 6330 = splice donor site
6331 - 6336 = unique BamHI restriction site for cloning of immunoglobulin variable genes
6337 - 7388 = cDNA copy of human gamma-1 constant regions preceded by a 62 bp intron
7389 - 7709 = Arnie termination sequence

The human gamma-1 constant region used in this construct has a $G1m^{Non-a}$ allotype which is defined by a Glutamic acid (E) residue at position 356 (according to Eu numbering) and a Methionine (M) residue at position 358 (according to Eu numbering). These two residues are underlined in the sequence above.

Fig. 34. *Heavy (panel A) and light (panel B) chains RNA splicing events taking place during antibody F19 expression in mammalian cells* - schematic overview.

A. Heavy chain RNA splicing

B. Kappa light chain RNA splicing

Fig. 35. *Concentration dependence of L_AH_C supernatant binding to CD8-FAP.*

Fig. 36. *Binding of biotinylated L_AH_C to human FAP.*

Fig. 37. *CD8-FAP carries the F19 epitope as detected with cF19.*

Examples

Example 1: **Construction of mouse - human chimeric genes**

[0078] The chimeric F19 (cF19) antibody was designed to have the mouse F19 V_L and V_H regions linked to human kappa and gamma-1 constant regions, respectively. PCR primers were used to modify the 5'- and 3'- sequences flanking the cDNA sequences coding for the mouse F19 V_L and V_H regions (Table 1). PCR primers specific for F19 light chain V-region were designed. These adapted mouse F19 variable regions were then subcloned into mammalian cell expression vectors already containing the human kappa (pKN100 vector) or gamma-1 (pG1D105 vector) constant regions (Figure 23).

[0079] These vectors employ the human cytomegalovirus (HCMV) promoter/enhancer to efficiently transcribe the light and heavy chains. The vectors also contain the SV40 origin of replication to permit efficient DNA replication and subsequent protein expression in cos cells. The expression vectors were designed to have the variable regions inserted as HindIII-BamHI DNA fragments. PCR primers were designed to introduce these restrictions sites at the 5'- (HindIII) and 3'- (BamHI) ends of the cDNAs coding for the V-regions. In addition the PCR primers were designed to introduce the Kozak sequence (GCCGCCACC) at the 5'-ends of both the light and heavy chain cDNAs to allow efficient translation (Kozak M.: At least six nucleotides preceding the AUG initiator codon enhance translation in mammalian cells. *J. Mol. Biol.* (1987) **196**: 947), and to introduce splice donor sites at the 3'-ends of both the light and heavy chain cDNAs for the variable regions to be spliced to the constant regions. The PCR primers used in the construction of the chimeric F19 light and heavy chains are shown in Table 1. The DNA and amino acid sequences of the mouse F19 V_L and V_H regions as adapted for use in the construction of chimeric F19 light and heavy chains are shown in Figures 24 and 25. The DNA sequences of mouse F19 light and heavy chains cloned into the eukaryotic expression vectors pKN100 and pG1D105, respectively, are shown in Figures 26 and 27.

TABLE 1: PCR primers for the construction of chimeric F19 antibody.

A. Light chain variable region

1. Primer for the construction of the 5'-end (37mer)

5' CAGA **AAGCTT** GCCGCCACC ATG GAT TCA CAG GCC CAG 3'

HindIII Kozak sequence M D S Q A Q

2. Primer for the construction of the 3'-end (35mer)

5' CCGA **GGATCC** ACTCACG TTT CAG CTC CAG CTT GGT 3'

BamHI Splice donor site

B. Heavy chain variable region

1. Primer for the construction of the 5'-end (37mer)

5' CAGA **AAGCTT** GCCGCCACC ATG GGA TGG AGC TGG GTC 3'

HindIII Kozak sequence M G W S W V

2. Primer for the construction of the 3'-end (35mer)

5' CCGA **GGATCC** ACTCACC TGA GGA GAC GGT GAC TGA 3'

BamHI Splice donor site

Example 2: **Expression and binding activity of chimeric F19 antibody**

[0080] The two plasmid DNAs coding for the chimeric F19 light and heavy chains (see example 1) were co-transfected into cos cells to look for transient expression of chimeric F19 antibody as described below. After 72 h incubation, the medium was collected, centrifuged to remove cellular debris, and analysed by ELISA for the production of a human IgG1-like antibody. The cos cell supernatant containing the chimeric F19 antibody was analysed for its ability to bind to HT 1080 cells (see example 13) expressing the FAP antigen on their surface.

Transfection of *cos* cells using electroporation

[0081] The mammalian expression vectors pg1d105 and pKN100 containing the chimeric or reshaped human heavy and light chains versions, respectively, were tested in cos cells to look for transient expression of F19 antibodies. Cos

7 cells were passaged routinely in DMEM (Gibco BRL cat. #41966) containing penicillin (50 IU/ml), streptomycin (50μg/ml), L-glutamine and 10% heat-inactivated gamma globulin-free foetal calf serum (FCS, Harlan Sera-Lab cat. # D0001). The DNA was introduced into the cos cells by electroporation using the Gene Pulsar apparatus (BioRad). DNA (10μg of each vector) was added to a 0.8ml aliquot of $1x10^7$ cells/ml in Phosphate-buffered saline (PBS, Ca^{2+} and Mg^{2+} free). A pulse was delivered at 1,900 volts, 25μF capacitance. After a 10 min recovery period at ambient temperature the electroporated cells were added to 8 ml of DMEM containing 5% FCS. After 72h incubation at 37°C, the medium was collected, centrifuged to remove cellular debris, and stored under sterile conditions at 4°C for short periods of time, or at -20°C for longer periods.

ELISA method for measuring assembled IgG1/kappa antibody concentrations in *cos* cell supernatants

[0082] Samples of antibodies produced in transfected *cos* cells were assayed by ELISA to determine how much reshaped human antibody had been produced. For the detection of human antibody, plates were coated with goat anti-human IgG (Fcγ fragment specific) antibody (Jackson ImmunoResearch Laboratories Inc., #109-005-098). The samples from *cos* cells were serially diluted and added to each well. After incubation for 1h at 37°C and washing, horseradish peroxidase conjugated goat anti-human kappa light chain (Sigma, A-7164) was added. After incubation for 30 mins at 37°C and washing, K-blue substrate (mixer of 3,3',5,5' tetramethylbenzidine and hydrogen peroxide, Bionostics Limited, #KB175) was added. After standing at room temperature for 30 mins, the reaction was stopped using Red Stop solution (Bionostics Limited, #RS20) and the optical density read on a microplate reader at 650 nm. Purified human IgG1/Kappa antibody (Sigma, I-3889) of known concentration was used as a standard.

[0083] The expression of chimeric F19 antibody in *COS* cells was poor (Table 2), between 10 and 60 ng/ml which is at least 10 fold less than most antibodies.

[0084] In an attempt to increase expression levels of the chimeric F19 antibody, the leader sequence of F19 V_L region was changed by substitution of Leucine to Proline at position -9. This single change in amino acid in the leader sequence resulted in at least doubling the amount of chimeric antibody produced in COS cells.

[0085] The test results show that chimeric F19 binds specifically and with the expected avidity to the FAP target.

TABLE 2

Chimeric F19 antibody concentrations in *COS* cell supernatants (These are the results of three independent transfections)		
Transfected Antibody components		Human γ1/K
Heavy chain	Kappa light chain	[in μg/ml]
cF19	cF19 (F19 leader sequence)	0.060
cF19	cF19 (mutated leader sequence)	0.212
cF19	cF19 (F19 leader sequence)	0.056
cF19	cF19 (mutated leader sequence)	0.108
cF19	cF19 (F19 leader sequence)	0.011
cF19	cF19 (mutated leader sequence)	0.087

***Example 3:* Construction of the reshaped human F19 light chain versions a to c (La-Lb)**

[0086] The construction of the first version of reshaped human F19 V_L region (La) was carried out using overlapping PCR fragments in a method similar to that described by Daugherty B. L., DeMartino J. A., Law M. F., Kawka D. W., Singer I. I. and Mark G. E. (1991) Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins. *Nucl.* Acids Res. **19**: 2471. Ten oligonucleotides were synthesised that consisted of five primer pairs, APCR1-vla1, vla2-vla3, vla4-vla5, vla6-vla7, and vla8-APCR4 (Table 3 and Figure 28). There was an overlapping sequence of at least 21 bases between adjacent pairs (Figure 28). APCR1 and APCR4 hybridised to the flanking pUC19 vector sequences. The mutagenic primers were designed such that their 5' end immediately followed the wobble position of a codon. This strategy was used to counteract the gratuitous addition of one nucleotide to the 3' end of the strand complementary to the mutagenic primer by the DNA polymerase during PCR (Sharrocks A. D. and Shaw P. E. (1992) Improved primer design for PCR-based, site-directed mutagenesis. *Nucl. Acids Res.* **20**: 1147). The appropriate primer pairs (0.2μM of each) were combined

with 10ng of version "b" of reshaped human L25V_L region cDNA, and 1 unit of AmpliTaq (Perkin Elmer Cetus) DNA polymerase in 50μl of PCR buffer containing 10mM Tris-HCl (pH8.3), 50mM KCl, 200μM dNTPs, and 1.5mM $MgCl_2$. This was overlaid with mineral oil and PCR was performed for 25 cycles, each cycle consisting of a denaturation step at 94°C for 1 min, a primer annealing step at 55°C for 1 min, and an extension step at 72°C for 2 mins. This was followed by a single cycle consisting of a further elongation step at 72°C for 10 mins followed by cooling to 4°C. The ramp time between the primer-annealing and extension steps was 2.5 mins. The PCR products of the five reactions (A, B, C, D and E) were then purified by gel electrophoresis followed by DNA elution using Wizard PCR preps (Promega). PCR products A, B, C, D, and E were assembled by their complementarity to one another. In the second set of PCR reactions, PCR products B and C, and D and E, (50ng of each) were added to 50μl PCR reactions (as described above) each containing 1 unit of AmpliTaq (Perkin Elmer Cetus) DNA polymerase. The reactions were cycled for 20 cycles as described above with the exception that the annealing temperature was raised to 60°C. In the third set of PCR reactions, PCR products F and G were PCR-amplified using 1 μl of each prior PCR reaction and the appropriate pair of PCR primers (vla2-vla5 or vla6-APCR4). The PCR reactions contained 1 unit of AmpliTaq DNA polymerase in 50 μl PCR reaction (as described above) and were amplified for 25 cycles as in the first stage. In the fourth set of PCR reactions, the PCR product H was PCR-amplified using 1 μl of each prior PCR reaction and the vla2-APCR4 pair of PCR primers. Finally, PCR products A and H were assembled by their own complementarity in a two step-PCR reaction similar to that described above using RSP and UP as the terminal primers. The fully assembled fragment representing the entire reshaped human F19 $V_L$region including a leader sequence was digested with HindIII and BamHI and cloned into pUC19 for sequencing. A clone having the correct DNA sequence was designated reshF19La (Figure 29) and was then subcloned into the eukaryotic expression vector pKN100. The DNA sequence of reshF19La cloned into pKN100 is shown in Figure 30.

[0087] The second version of reshaped human F19 $V_L$region (Lb) was constructed using the same scheme as that described for La but where vla4 and vla7 primers were substituted by vlb4 and vlb7 respectively (Table 3). The DNA sequence of Lb is shown in Figure 29.

[0088] The third version of reshaped human F19 $V_L$region (Lc) was constructed using the QuikChange™ site-directed mutagenesis kit from Stratagene. The QuikChange site-directed mutagenesis method was performed according to the manufacturer's instructions, using reshF19La in pKN100 vector as double stranded DNA template. The mutagenic oligonucleotide primers F19Lc-sense and F19Lc-antisense (Table 3) for use in this protocol were designed according to the manufacturers instructions. Briefly, both the mutagenic primers contained the desired point mutation (codon TTT at Kabat residue position 49 (Phe) changed to TAT coding for Tyr) and annealed to the same sequence on opposite strands of La in pKN100 vector. The point mutation was verified by DNA sequencing the entire V_L region. The DNA sequence of Lc is shown in Figure 29. To eliminate the possibility that random mutations occurred in the pKN100 during the PCR reaction, the $V_L$region was cut out of the pKN100 vector as an HindIII/BamHI fragment and re-subcloned into an unmodified pKN100 vector cut with the same two restriction enzymes beforehand.

TABLE 3: PCR primers for the construction of reshaped human F19 light chain variable regions

1. Primers for the synthesis of version "a"

F19vla1 (36 mer):

5' GTCATCACAATGTCTCCGGAGGAACCTGGAACCCAG 3'

F19vla2 (29 mer):

5' CTCCGGAGACATTGTGATGACCCAATCTC 3'

F19vla3 (45 mer):

5' GAATATAAAAGGCTCTGACTGGACTTGCAGTTGATGGTGGCCCTC 3'

F19vla4 (72 mer):

5' CAGTCAGAGCCTTTTATATTCTAGAAATCAAAAGAACTACTTGGCCTGGTAT CAGCAGAAACCAGGACAGCC 3'

F19vla5 (44 mer):

5' ACCCCAGATTCCCTAGTGCTAGCCCAAAAGATGAGGAGTTTGGG 3'

F19vla6 (67 mer):

5' TAGCACTAGGGAATCTGGGGTACCTGATAGGTTCAGTGGCAGTGGGTTTG GGACAGACTTCACCCTC 3'

F19vla7 (53 mer):

5' GTCCCTTGTCCGAACGTGAGCGGATAGCTAAAATATTGCTGACAGTAA TAAAC 3'

F19vla8 (33 mer):

5' GCTCACGTTCGGACAAGGGACCAAGGTGGAAAT 3'

2. Primers for the synthesis of version "b"

F19vlb4 (72 mer):

5' CAGTCAGAGCCTTTTATATTCTAGAAATCAAAAGAACTACTTGGCCTGG TTCCAGCAGAAACCAGGACAGCC 3'

F19vlb7 (57 mer):

5' GTCCCTTGTCCGAACGTGAGCGGATAGCTAAAATATTGCTGACAGTCATA AACTGCC 3'

3. Primers for the synthesis of version "c"

F19Lc-sense (34 mer):

5' CCCAAACTCCTCATCTATTGGGCTAGCACTAGGG 3'

F19Lc-antisense (34 mer):

5' CCCTAGTGCTAGCCCAATAGATGAGGAGTTTGGG 3'

4. Primers hybridizing to the flanking PUC19 vector sequences

APCR1 (17 mer, sense primer):	5' TACGCAAACCGCCTCTC 3'
APCR4 (18 mer, anti-sense primer):	5' GAGTGCACCATATGCGGT 3'
RSP (-24) (16 mer, sense primer):	5' AACAGCTATGACCATG 3'
UP (-40) (17 mer, anti-sense primer):	5' GTTTTCCCAGTCACGAC 3'

Example 4: **Construction of the reshaped human F19 heavy chain versions a to e (Ha-He)**

[0089] Version "a" of reshaped human F19 V_H regions (Ha) was constructed using the same PCR methods as described for the construction of version "a" of reshaped human F19 $V_L$region (La) (Figure 31). The template DNA was version "a" of reshaped human 226 V_H (Léger O. J. P., Yednock T. A., Tanner L., Horner H. C., Hines D. K., Keen S., Saldanha J., Jones T., Fritz L. C. and Bendig M. M. (1997). Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis. *Hum. Antibod.* **8**: 3). Six PCR primers were designed and synthesized for the construction of version "a" of reshaped human F19 V_H region (Table 4). PCR products A, B, C, and D were obtained using APCR1-Vha1, Vha2-Vha3, Vha4-Vha5 and Vha6-APCR4 as PCR primer pairs, respectively. The PCR conditions were essentially as described for the construction of reshaped human F19 $V_L$region. A clone having the correct DNA sequence was designated reshF19Ha (Figure 32) and was then subcloned into the eukaryotic expression vector pG1D105. The DNA sequence of reshF19Ha cloned into pG1D105 is shown in Figure 33.

[0090] The third version of reshaped human F19 V_H region (Hc) was constructed using the same scheme as that described for Ha but where Vha4 primer was substituted by Vhc4 (Table 4). The DNA sequence of Hc is shown in Figure 32. The second (Hb) and fourth (Hd) version of reshaped human F19 V_H region were constructed based on the PCR-mutagenesis methods of Kamman et al. (Kamman M., Laufs J., Schell J. and Gronenborn B. (1989) Rapid insertional mutagenesis of DNA by polymerase chain reaction (PCR). *Nucl. Acids Res.* **17**: 5404). For Hb and Hd, a mutagenic primer F19VHbd6 (Tyr-91 to Phe-91, Table 4) was used paired with APCR4 in PCR reactions with Ha and Hc as the template DNA, respectively. The PCR products VHb and VHd were restriction enzyme digested with PstI and BamHI and subcloned into reshF19Ha and reshF19Hc, respectively, previously digested with the same two restriction enzymes. The DNA sequences of Hb and Hd are shown in Figure 32.

[0091] Version e of reshaped human F19 V_H region (He) was constructed based on the PCR-mutagenesis methods of Kamman *et al.* (1989) already mentioned above:

[0092] For reshF19He mutagenic primer F19MsclHe (Table 5) was used paired with primer F19V_HHindIII (Table 5) in PCR reactions with Hc cloned in pg1d105 mammalian expression vector as the template DNA. The appropriate primer pairs (0.2μM of each) were combined with 10ng of cDNA of version "a" of reshaped human 226 V_H region in 100μl of PCR buffer containing 10mM KCl, 10mM $(NH_4)_2SO_4$, 20mM Tris-HCl (pH 8.8) 2mM $MgSO_4$, 0.1% Triton X-100 and 200μM dNTPs. Reaction mixtures were overlaid with mineral oil and kept at 94°C for 5 mins. Then 1 unit of Deep Vent DNA polymerase (New England Biolabs) was added ("Hot Start" PCR; Chou Q., Russell M., Birch D., Raymond J. and Bloch W. (1992) Prevention of pre-PCR mis-priming and primer dimerization improves low-copy-number amplifications. *Nucl. Acids Res.* **20**: 1717) and PCR was performed for 25 cycles on a TRIO-Thermoblock Thermal Cycler (Biometra, Göttingen, Germany). Each cycle consisting of a denaturation step at 94°C for 1 min, a primer annealing step at 70°C for 1 min, and an extension step at 72°C for 2 mins. This was followed by a single cycle consisting of a further elongation step at 72°C for 10 mitts followed by cooling at 4°C. The PCR products were then extracted and purified from a TAE 1.4% standard agarose gel using a QIAquick™ gel extraction kit, following the protocol supplied by the manufacturer

(QIAGEN Ltd., UK). The PCR product V_He was then restriction enzyme digested with MscI and HindIII and ligated into reshF19Hc cloned in pg1d105 previously digested with the same two restriction enzymes. The MscI restriction recognition site is unique to all the reshaped human F19 V_H region versions and is not present in the pg1d105 expression vector. The HindIII restriction recognition site is a unique site in pg1d105 for clotting of V_H immunoglobulin genes.

[0093] Electroporation-competent XL-1 Blue E. coli cells were transformed with 1 μl of the ligated DNA and plated on agarose plates containing Ampicillin. Colonies were then screened for the presence and correct size of inserts by direct PCR on colonies (Güssow D. and Clackson T. (1989) Direct clone characterization from plaques and colonies by the polymerase chain reaction. *Nucl. Acids Res.* **17**: 4000) with primers HCMi and Hucγ1 hybridising to the flanking pg1d105 vector sequences (Table 5). DNA from positive colonies was prepared using a Plasmid Midi kit, following the protocol supplied by the manufacturer (QIAGEN Ltd., UK). DNA sequencing was performed by the dideoxy chain termination method (Sanger F., Nicklen S. and Coulson A. (1977) DNA sequencing with chain-terminating inhibitors. *Proc. natn. Acad. Sci. U. S. A.* **74:** 5463) directly from circular vector DNA using conventional heat denaturation (Andersen A., Pettersson A. and Kieldsen T. (1992) A fast and simple technique for sequencing plasmid DNA with sequenase using heat denaturation. *Biotechniques* **13:** 678) and Sequenase 2.0 (USB, Cleveland, OH). The DNA sequences of reshF19He is shown in Figure 32.

TABLE 4: PCR primers for the construction of reshaped human F19 heavy chain variable regions versions a to d.

1. Primers for the synthesis of version "a"

F19vha1 (47mer):

5' GTGTATTCAGTGAAGGTGTATCTACTAGTTTTACAGCTGACTTTCAC 3'

F19vha2 (53 mer):

5' TAGTAGATACACCTTCACTGAATACACCATACACTGGGTTAGACAGG CCCCTG 3'

F19vha3 (71 mer):

5' CCCTTGAACTTCTGGTTGTAGTTAGGAATACCATTGTTAGGATTAATACC TCCTATCCACTCCAGCCTTTG 3'

F19vha4 (71 mer):

5' TAACTACAACCAGAAGTTCAAGGGCCGGGCCACCTTGACCGTAGGCAA GTCTGCCAGCACCGCCTACATGG 3'

F19vha5 (63 mer):

5' GCATGGCCCTCGTCGTAACCATAGGCGATTCTTCTTCTGGCGCAGTAGT AGACTGCAGTGTCC 3'

F19vha6 (48 mer):

5' CTATGGTTACGACGAGGGCCATGCTATGGACTACTGGGGTCAAGGAAC 3'

2. Primers for the synthesis of version "c"

F19vhc4 (71 mer):

5' TAACTACAACCAGAAGTTCAAGGGCCGGGTCACCATCACCGTAGACA CCTCTGCCAGCACCGCCTACATGG 3'

3. Primers for the synthesis of version "b" and "d"

F19vhbd6 (27 mer):

5' GGACACTGCAGTCTACTTCTGCGCCAG 3'

4. Primers hybridizing to the flanking PUC19 vector sequences

APCR1 (17 mer, sense primer): 5' TACGCAAACCGCCTCTC 3'

APCR4 (18 mer, anti-sense primer): 5' GAGTGCACCATATGCGGT 3'

TABLE 5: PCR primer for the construction of reshaped human F19 heavy chain variable regions version e

1. Primer for the synthesis of version "e"

F19MscIHe (65 mer, anti-sense):

5' CCTT*TGGCCA*GGGGCCTGTCTAACCCAGTGTATGGTGTATTCAGTGAAGGTG
MscI
TATCCACTAGTTTCCACTAGTTT 3'

2. Primers hybridizing to the flanking pg1d105 mammalian expression vector sequences

HCMi (28 mer, sense): 5' GTCACCGTCCTTGACACGCGTCTCGGGA 3'
Hucγ1 (17 mer, anti-sense): 5' TTGGAGGAGGGTGCCAG 3'

Example 5: **Reshaped human F19 antibody concentrations in *COS* cells supernatants**

[0094] *COS* cells were transfected with one pair of a series of reshaped human F19 antibody constructs and the human antibody concentration was measured using the IgG1/Kappa ELISA as described in example 2.

TABLE 6

Reshaped human F19 antibody concentrations in *COS* cell supernatants		
Transfected Antibody components		**Human γ1/K**
Heavy chain	**Kappa light chain**	**concentration [μg/ml]**
Ha	La	2.50
Ha	Lb	0.18
Hb	La	1.25
Hb	Lb	0.10
Hd	La	1.15
Hd	Lb	0.18
Ha	La	1.50
Ha	Lc	1.56

TABLE 6 (continued)

Reshaped human F19 antibody concentrations in *COS* cell supernatants		
Transfected Antibody components		Human γ1/K
Heavy chain	Kappa light chain	concentration [μg/ml]
Hc	La	1.47
Hc	Lc	1.97
cF19	La	1.54
cF19	Lb	0.07
cF19	Lc	2.14

TABLE 7

Reshaped human F19 antibody concentrations in *COS* cell supernatants		
Transfected Antibody components		Human γ1/K
Heavy chain	Kappa light chain	concentration [μg/ml]
Ha	La	2.00
Ha	Lc	2.50
Hc	La	2.90
Hc	Lc	3.00
He	La	2.80
He	Lc	3.50

RNA splicing events required for the expression of immunoglobulin genes in mammalian cells

[0095] Both mammalian expression vectors pKN100 and pg1d105 have an intron between the variable and the constant regions which is removed during the process of gene expression to give rise to an messenger RNA. The splicing event which consists of a DNA recombination between the heavy or light chain splice donor sites and the immunoglobulin splice acceptor site is described in Figure 34.

Example 6: Flow cytometric analysis of the binding of cF19 and L_AH_C to FAP-expressing human cells

[0096] The ability of L_AH_C to bind to both recombinant and endogenously expressed FAP on cell surface was tested.

[0097] The example was conducted to determine the binding of L_AH_C to cellular FAP. Both naturally FAP expressing MF-SH human tumour cells and FAP-transfected human tumour cell lines were used as cellular targets. L_AH_C was studied in cytofluorometric assays evaluating direct binding to target cells as well as by the inhibitory effect on the binding of either murine F19 or chimeric cF19 anti-FAP antibodies.

[0098] Antibodies and cell lines used were F19 (murine monoclonal anti-human FAP antibody, IgG1 subclass), mIgG (murine immunoglobulin, IgG class), cF19 (chimeric monoclonal anti-human FAP antibody, IgG1 subclass), L_AH_C (reshaped monoclonal anti-human FAP antibody, IgG1 subclass), hIgG1 (human immunoglobulin, IgG1 subclass), MF-SH (human malignant fibrous histiocytoma cell line), HT-1080 (human fibrosarcoma cell line), HT-1080FAP clone 33 (HT-1080 cell line transfected with cDNA encoding human FAP)

Direct binding of L_AH_C to FAP on the surface of human tumour cell lines

[0099] $5x10^5$ cells of the tumour cell line under investigation were incubated with the indicated concentration of test or control antibody in a total volume of 0.2 ml phosphate-buffered saline (PBS) supplemented with 1% bovine serum albumin (BSA) for 30 min on ice.

[0100] Subsequently, cells were washed twice with 2 ml of PBS, resuspended in 0.2 ml of PBS supplemented with 1% BSA, the appropriate anti-Ig-antibody as secondary reagent (either a 1:20 dilution of goat anti-mouse Ig FITC-labeled [Dianova] or a 1:20 dilution of mouse anti-human IgG FITC-labeled [Dianova]) and incubated for another 30 min on ice.

[0101] Cells were again washed twice with 2 ml of PBS, resuspended in a total volume of 0.5 ml of PBS supplemented with 1% paraformaldehyde (PFA) and kept on ice. Single cell fluorescence was determined cytofluorometrically by analysing the cellular green fluorescence in the 488nm light of an EPICS XL (Coulter).

Inhibitory effect of L_AH_C on binding of biotinylated cF19 to FAP on the surface of human cell lines

[0102] $5x10^5$ cells of the tumour cell line under investigation were incubated with the indicated concentration of the biotin-labelled antibody in a total volume of 0.2 ml PBS supplemented with 1% BSA and the simultaneously added unlabelled test or control antibody for 30 min on ice. Subsequently, cells were washed twice with 2 ml of PBS, resuspended in 0.2 ml of PBS supplemented with 1% BSA, 1:40 diluted streptavidin-FITC (Dianova) as secondary reagent and incubated for another 30 min on ice.

[0103] Alternatively, cells were incubated with the indicated concentrations of murine F19 and cell-bound antibody detected via 1:20 diluted goat anti-mouse Ig labelled with FITC by comparable incubation steps.

[0104] In each case, cells were finally washed twice with 2 ml of PBS, resuspended in a total volume of 0.5 ml PBS supplemented with 1% PFA and kept on ice. Single cell fluorescence was determined cytofluorometrically by analysing the cellular green fluorescence in the 488nm light of an EPICS XL (Coulter).

[0105] Both, cF19 and L_AH_C bind in a concentration dependent manner specifically to to FAP-transfected HT-1080FAP clone33 human tumour cells (Table 8). No binding toFAP-negative HT-1080 cells was detectable (Table 9). Both cF19 and L_AH_C bound in a concentration dependent manner to human MF-SH cells endogenously expressing FAP (Table 10).

[0106] Biotinylated cF19 in a concentration dependent manner bound to human HT-1080FAP clone 33 (Table 11). No binding was detectable to FAP-negative HT-1080 cells (Table 12).

[0107] Binding of biotinylated cF19 to HT-1080FAP clone 33 cells was inhibited by both unlabelled cF19 and unlabelled L_AH_C (Table 13).

[0108] Chimeric anti-human FAP monoclonal antibody cF19 as well as reshaped human anti-human FAP monoclonal antibody L_AH_C (example 10) were shown to bind directly to FAP expressed on human cell lines either endogenously expressing this protein or transfected with cDNA encoding for it. This binding was shown to be concentration dependent. Binding of biotinylated cF19 could be inhibited by both unlabelled cF19 and unlabelled L_AH_C.

[0109] Using cytofluorometric technology, direct binding as well as inhibition of specifically binding ragents showed specificity of chimeric cF19 and reshaped L_AH_C human monoclonal antibodies to cell surface expressed FAP.

Table 8

Binding of anti-FAP antibodies to HT-1080FAP clone 33 cells			
Concentration of antibody	Mean fluorescence intensity		
[ng/mL]	hIgG1	cF19	L_AH_C
500.0	0.12	6.65	2.76
100.0	0.12	1.63	0.66
20.0	0.12	0.43	0.22
4.0	0.12	0.17	0.15
0.8	0.12	0.14	0.13

Table 9

Binding of anti-FAP antibodies to non-transfected HT-1080 cells			
Concentration of antibody	Mean fluorescence intensity		
[ng/mL]	hIgG1	cF19	L_AH_C
500.0	0.11	0.11	0.12
100.0	0.11	0.11	0.11
20.0	0.11	0.11	0.12
4.0	0.11	0.11	0.12
0.8	0.11	0.11	0.11

Table 10

Binding of anti-FAP antibodies to MF-SH cells			
Concentration of antibody	Mean fluorescence intensity		
[ng/mL]	hIgG1	cF19	L_AH_C
4.0	0.6	3.6	2.8
2.0	n.d.	3.3	2.5
1.0	n.d.	2.4	1.9
0.5	n.d.	1.8	1.3

n.d.: not done

Table 11

Binding of biotinylated cF19 antibody to HT-1080FAP clone 33 cells		
Concentration of antibody	Mean fluorescence intensity	
[ng/ml]	Biotinylated hIgG1	Biotinylated cF19
5,000.0	0.2	36.5
1,000.0	0.2	18.1
200.0	0.2	4.5
40.0	0.2	1.3
8.0	0.2	0.5
1.6	0.3	0.3

Table 12

Binding of biotinylated cF19 antibody to non-transfected HT-1080 cells		
Concentration of antibody	Mean fluorescence intensity	
[ng/ml]	Biotinylated hIgG1	Biotinylated cF19
5,000.0	0.1	0.1
1,000.0	0.1	0.1
200.0	0.1	0.1
40.0	0.1	0.1
8.0	0.1	0.1
1.6	0.1	0.1

Table 13

Competition of anti-FAP antibodies with the binding of biotinylated cF19 to HT-1080FAP clone 33 cells		
	Concentration of competitor antibody	Mean fluorescence concentration
Competitor antibody	[μg/mL]	
no	0.00	11.2
hIgG1	1.00	9.0
hIgG1	3.16	11.3
hIgG1	10.00	9.8
hIgG1	31.66	10.3
cF19	1.00	7.5
cF19	3.16	4.8
cF19	10.00	1.3
cF19	31.66	1.2
L_AH_C	1.00	8.0
L_AH_C	3.16	5.5
L_AH_C	10.00	2.9
L_AH_C	31.66	1.7
Biotinylated cF19 was used at a concentration of 1 μg/mL in all tests shown in the table.		

Example 7: **In vitro immune effector functions of monoclonal antibody L_AH_C**

[0110] This experiment was conducted to determine the potential of the monoclonal antibody (mab) L_AH_C with specificity for fibroblast activation antigen (FAP) to lyse FAP-expressing targets in the presence of human complement or human mononuclear leukocytes, respectively.

[0111] In particular, the ability of L_AH_C to mediate cytotoxic effects against HT-1080FAP clone 33 cells, which expressed human FAP on the surface, was studied. Cytotoxicity was determined in vitro using the following approach: ^{51}Cr-labelled target cells were incubated in the presence of L_AH_C with human serum as source of complement or human MNC (peripheral blood mononuclear cells) as effectors. Release of ^{51}Cr war measured as measure of target-cell lysis.

[0112] Antibodies and cell lines used were L_AH_C (reshaped human anti-human FAP IgG1 antibody), hIgG1 (human IgG1 isotype control), 3S193 (murine monoclonal anti-Lewis^y IgG3 antibody), mIgG (murine IgG control), HT-1080 (human fibrosarcoma), HT-1080FAP clone 33, (HT1080 transfected with cDNA encoding human FAP), MCF-7 (human breast adenocarcinoma cell line).

Complement-mediated lysis of target cells by L_AH_C

[0113] Tumour cells were radiolabelled by incubation in RPMI1640 medium with 100 µl ^{51}Cr (NEN) at 37° C for one hour. Subsequently, cells were washed twice in ^{51}Cr-free medium and resuspended at a concentration of $2x10^5$ cells per mL.

[0114] Human serum as source of complement was freshly prepared from blood of different volunteers. Blood was taken by puncturing the arm vein, remained at room temperature for one hour to allow clotting to occur, and was kept at 4° C over night. Serum was seperated by centrifugation and taken off from the sediment.

[0115] The antibody under study was diluted from the stock solution to the appropriate concentration in RPMI1640 cell culture medium.

[0116] $1x10^4$ radiolabelled tumour cells of the indicated cell line were incubated in the presence of different concentrations of test or control antibody and 25% of the human serum used as source of complement for 2 h at 37° C in a 95% air and 5% CO_2 incubator. Incubation was performed in U-shaped 96-well plates in a total volume of 200 µl RPMI1640 and done in triplicate. After the incubation period, plates were centrifugated, 100 µl of the supernatant were taken off and radioactivity was determined in a gamma-counter. Total number of incorporated radioactivity was determined by measuring 10^4 target cells. Spontaneous release was defined as activity released from the target cells in the absence of both antibody and complement during the described incubation period.

[0117] Specific lysis was calculated as follows:

$$\text{specific lysis (in \%)} = \frac{[\text{activity sample}] - [\text{activity spontaneous release}]}{[\text{maximum activity}] - [\text{activity spontaneous release}]} \times 100$$

Antibody-dependent cellular cytotoxicity (ADCC) of L_AH_C

[0118] Tumour cells were radiolabelled by incubation in RPMI1640 medium with 100 µl ^{51}Cr at 37°C for one hour. Subsequently, cells were washed twice in ^{51}Cr-free medium and resuspended at a concentration of $2x10^5$ cells per mL.

[0119] MNC (peripheral blood mononuclear cells) were prepared from peripheral blood taken by puncturing the arm vein of different healthy human volunteers. Clotting was prevented by the addition of 20% citrate buffer. MNC from 4 mL of this blood preparation were purified by centrifugation (30 min at 400 G and room temperature) on 3 mL of lymphocyte preparation medium (Boehringer Mannheim, Germany). MNC (peripheral blood mononuclear cells) were taken off from the gradient, washed three times and diluted with RPMI1640 to the appropriate concentration. Lymphocyte activated killer (LAK) cells were derived from MNC (peripheral blood mononuclear cells) by incubation for 5 days at 37° C in an 95% air and 5% CO_2 incubator at an initial density of $1.3x10^6$ cells per mL in the presence of 100U recombinant human Interleukin-2 (IL-2). The antibody under study was diluted from the stock solution to the appropriate concentration in RPMI1640 cell culture medium.

[0120] $1x10^4$ radiolabelled tumour cells of the indicated cell line were incubated for 5 h at 37°C and 5%CO_2 in the presence of different concentrations of test or control antibody and MNC (peripheral blood mononuclear cells) in a number necessary to reach the indicated effector:target cell ratio. Incubation was performed in U-shaped 96-well plates in a total volume of 200 µl RPMI1640 and done in duplicate.

[0121] After the incubation period, plates were centrifugated, 100 µl of the supernatant were taken off and radioactivity was determined in a gamma-counter. Total number of incorporated radioactivity was determined by measuring 10^4

target cells. Spontaneous release was defined as activity released from the target cells in the absence of both antibody and effector cells during the described incubation period.

[0122] Specific lysis was calculated as follows:

$$\text{specific lysis (in \%)} = \frac{[\text{activity sample}] - [\text{activity spontaneous release}]}{[\text{maximum activity}] - [\text{activity spontaneous release}]} \times 100$$

Antibody mediated complement lysis of tumour cells

[0123] No complement mediated lysis above control was seen in HT-1080FAP clone 33 cells with L_AH_C up to a concentration of 50 μg/mL (Table 14, Table 15a)

[0124] Lytic activity of human serum used as source of complement was shown by lysis of MCF-7 human breast carcinoma cells in the presence of 12.5 μg/mL 3S193, a murine monoclonal anti-Lewis^y antibody with known complement activating ability (Table 15b)

Antibody mediated cellular lysis of tumour cells

[0125] In the presence of L_AH_C in a concentration of up to 10 μg/mL, no lysis of HT-1080FAP clone 33 above isotype control was detectable in ADCC mediated by human MNC (peripheral blood mononuclear cells, Table 16) or human LAK cells (lymphokine activated killer cell) (Table 17) at an effector:target ratio of 50:1:

[0126] In appropriate in vitro assays with either human complement or with human MNC (peripheral blood mononuclear cells) as effector mechanisms, human anti-FAP monoclonal antibody L_AH_C revealed no relevant cytotoxic effect above controls on FAP expressing tumor cell line HT-1080FAP clone 33.

[0127] In vitro, L_AH_C is unable to mediate cytotoxicity effected by human complement or human MNC (peripheral blood mononuclear cells) on a cell line positive for FAP, the antigen recognized by this antibody.

Table 14

Specific complement lysis (in %) of HT-1080FAP clone 33 tumor cell targets mediated by L_AH_C		
Source of human serum:	HT-1080 clone 33:	
concentration of antibody	hIgG1 isotype control	L_AH_C
A 50 μg/mL	5	4
A 10 μg/mL	5	3
B 50 μg/mL	7	5
B 10 μg/mL	6	5
0 μg/mL	0	0
Incubation: 2 hours at 37°C, 25% serum from human volunteers A or B, respectively, as source of complement.		

Table 15a

Specific complement lysis (in %) of HT-1080FAP clone 33 tumor cell targets mediated by human anti-FAP monoclonal antibody L_AH_C		
Source of human serum:	HT1080clone 33:	
concentration of antibody	hIgG1	L_AH_C
A 10.00 µg/ml	2	1
A 2.50 µg/ml	2	2
A 0.60 µg/ml	1	1
A 0.15 µg/ml	1	2
A 0.00 µg/ml	2	2
B 10.00 µg/ml	2	2
B 2.50 µg/ml	2	2
B 0.60 µg/ml	2	2
B 0.15 µg/ml	2	2
B 0.00 µg/ml	2	2
C 10.00 µg/ml	2	2
C 2.50 µg/ml	1	1
C 0.60 µg/ml	1	1
C 0.15 µg/ml	2	1
C 0.00 µg/ml	3	3
Incubation: 2 hours at 37°C, 25% serum from human volunteers A, B or C, respectively, as source of complement.		

Table 15b

Specific complement lysis (in %) of MCF-7 tumour cell targets mediated by murine anti-Lewis^y monoclonal antibody 3S193		
Source of human serum:	MCF-7:	
concentration of antibody	mIgG	3S193
A 10.00 µg/ml	0	21
A 2.50 µg/ml	1	21
A 0.60 µg/ml	0	21
A 0.15 µg/ml	1	18
A 0.00 µg/ml	0	0
B 10.00 µg/ml	1	13
B 2.50 µg/ml	0	17

Table 15b (continued)

Specific complement lysis (in %) of MCF-7 tumour cell targets mediated by murine anti-Lewis^y monoclonal antibody 3S193		
Source of human serum:	MCF-7:	
concentration of anti-body	mIgG	3S193
B 0.60 µg/ml	1	18
B 0.15 µg/ml	1	15
B 0.00 µg/ml	0	0
C 10.00 µg/ml	1	22
C 2.50 µg/ml	0	23
C 0.60 µg/ml	1	26
C 0.15 µg/ml	1	20
C 0.00 µg/ml	1	1
Incubation: 2 hours at 37° C, 25% serum from human volunteers A, B or C, as source of complement.		

Table 16

ADCC (antibody-dependant cellular cytotoxicity) (specific lysis in %) of HT-1080FAP clone 33 target cells by human MNC (peripheral blood mononuclear cells) mediated by L_AH_C.		
HT-1080FAP clone 33:		
Concentration of anti-body:	HT-1080FAP clone 33:	
[in µg/mL]	hIgG1	L_AH_C
10.000	2	2
2.500	2	2
0.625	2	2
0.156	3	3
0.000	3	3
Incubation: 5 hours at 37°C, 10^4 target cells and an effector:target cell ration of 50:1.		

Table 17

ADCC (antibody-dependenat cellular cytotoxicity, specific lysis in %) of HT-1080FAP clone 33 target cells by LAK cells (lymphokine activated killer cells) mediated by L_AH_C.		
Concentration of antibody:	HT-1080FAP clone 33:	
[in µg/mL]	hIgG1	L_AH_C
10.000	12	14
2.500	14	17
0.625	14	21
0.156	15	21
0.000	14	14
Incubation: 5 hours at 37°C, 10^4 target cells and an effector:target cell ration of 50:1.		

Example 8: **Immunohistochemical analysis of monoclonal antibody L_AH_C binding to normal and neoplastic human tissues**

[0128] This experiment was performed to determine the binding characteristics of the humanized mAb L_AH_C to normal and neoplastic human tissues.

[0129] The following antibodies were used: L_AH_C, cF19, and the negative control hu IgG1 were directly biotinylated according to methods of the state of the art and used at concentrations of 2.5 to 0.25 mg/ ml in 2% BSA/PBS (bovine serum albumin in phosphate-buffered saline). Murine mAb F19 was used as tissue culture supernatant of the F19 hybridoma, at dilutions of 1:5 to 1:10 in 2% BSA/PBS.

[0130] The following reagents were used for immunochemical assays: Streptavidin peroxidase complex (Vector Labs., Burlingame, CA, USA), Avidin-biotin peroxidase complex (Vector Labs.), Biotinylated horse anti-mouse (Vector Labs.), DAB (diaminobenzidine, Sigma Chemical Co. St. Louis, MO, USA), Harrris' hematoxylin.

[0131] Fresh frozen tissue samples examined included the following: Normal colon, breast, lung, stomach, pancreas, skin, larynx, urinary bladder, smooth and skeletal muscle.

[0132] Among the tumors tested were carcinomas from breast, colon, lung, esophagus, uterus, ovary, pancreas, stomach, and head and neck.

[0133] An indirect immunoperoxidase method was carried out according to state of the art methods (Garin-Chesa P, Old LJ, Rettig WJ: Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acd Sci USA 1990; 87:7235-7239) on five micrometer thickness fresh frozen sections.

[0134] DAB was used as a substrate for the final reaction product. The sections were counterstained with Harris' hematoxylin and examined for antigen expression.

L_AH_C expression in normal human tissues

[0135] The normal tissues tested were negative for L_AH_C expression, except for the normal pancreas in which a subset of positive endocrine cells in the islets of Langerhans (A cells) were identified with L_AH_C, cF19 and F19. (Table 18). No immunoreactivity was observed with the hu IgG1 (human immunoglobulin IgG1 subclass) used as a negative control.

L_AH_C expression in tumors

[0136] In the tumor samples, L_AH_C, cF19 and F19 showed an indistinguishable pattern of expression in the tumor stromal fibroblasts. A strong and homogeneous expression was found in the majority of the cases examined, especially in the cancer samples derived from breast, colon, lung, pancreas and in the squamous cell carcinomas (SQCC) of the head and neck tested (Table 19). No immunoreactivity was observed with the hu IgG1 used as negative control.

[0137] L_AH_C, cF19 and F19 showed immunoreactivity with the tumor stromal fibroblasts in the epithelial cancer samples tested. No L_AH_C or F19 immuno-reactivity was seen with either the fibrocytes of the normal organ mesenchyme or

the parenchymal cells of normal adult organs. The only exception was a subset of endocrine cells in the pancreatic islets, presumably glucagon-producing A cells, which react with the anti-FAP antibodies.

[0138] Immunohistochemical analysis of L_AH_C in normal human tissues and FAP-expressing human carcinomas showed indistinguishable patterns of binding for L_AH_C, cF19 and murine mAb F19.

Table 18

Immunoreactivity of mAbs L_AH_C, cF19 and F19 with normal human tissues				
Tissue type		L_AH_C	cF19	F19
Breast	-Duct epithelium	-	-	-
	-Myoepithelial cells	-	-	-
Colon	-Glandular epithelium	-	-	-
	-Smooth muscle	-	-	-
Lung	-Bronchial epithelium	-	-	-
	-Alveolar epithelium	-	-	-
Stomach	-Glandular epithelium	-	-	-
	-Smooth muscle	-	-	-
Urinary bladder	-Urothelium	-	-	-
	-Smooth muscle	-	-	-
Pancreas	-Exocrine acini	-	-	-
	-Endocrine islet cells	+ subset only	+subset only	+ subset only
Larynx -Squamous epithelium		-	-	-
Lymph node -Lymphocytes		-	-	-
Skeletal muscle-		-	-	-
Connective tissue		-	-	-
Skin	-Keratinocytes	-	-	-
	-Sweat glands	-	-	-

Table 19

Immunoreactivity of mAbs L_AH_C, cF19 and F19 with human tumor samples				
Tumor type	No.	L_AH_C	cF19	F19
Breast cancers (infiltrating ductal type)	7	7 Positive	7 Positive	7 Positive
Colon cancers (adenocarcinomas)	7	7 Positive	7 Positive	7 Positive
Lung carcinomas (adenocarcinoma (2) large cell type (2) squamous type (4)	8	7 Positive 1 Negative	7 Positive 1 Negative	7 Positive 1 Negative
Esophageal cancers (squamous type)	1	1 Positive	1 Positive	1 Positive
Endometrial cancers (adenocarcinoma)	1	1 Negative	1 Negative	1 Negative
Gastric cancers (adenocarcinoma)	2	2 Negative	2 Negative	2 Negative
Ovarian cancers (serous denocarcinoma)	2	1 Positive 1 Negative	1 Positive 1 Negative	1 Positive 1 Negative

Table 19 (continued)

Immunoreactivity of mAbs L_AH_C, cF19 and F19 with human tumor samples				
Tumor type	No.	L_AH_C	cF19	F19
Pancreatic cancers (adenocarcinomas)	2	2 Positive	2 Positive	2 Positive
Head and neck cancers (squamous cell type)	4	4 Positive	4 Positive	4 Positive
Abbreviations: No, number of cases from different patients studied; positive, number of cases showing antigen expression in the tumor stroma; negative, number of casestested that lacked detectable antigen expression.				

Example 9: **Species specificity of L_AH_C binding in tissue sections**

[0139] This experiment was conducted to assess the reactivity of L_AH_C with tissues from mouse, rat, rabbit and cynomolgus monkeys by immunohistochemical methods.

[0140] Also used in these tests were cF19 and huIgG1 as negative controls. The reagents used for immunohistochemistry were Streptavidin peroxidase complex (Vector Labs., Burlingame, CA, USA), DAB (Sigma Chemical Co., St. Louis, MO, USA) and Harris' hematoxylin.

[0141] The following fresh frozen tissue samples from mouse, rat, rabbit and cynomolgus were tested: Brain, liver, lung, kidney, stomach, pancreas, intestine, thymus, skin, muscle, heart, spleen, ovary, uterus and testes. As positive control, sections from normal human pancreas and a breast carcinoma sample were includded in every assay.

Immunohistochemistry

[0142] An indirect immunoperoxidase method was carried out as described in the state of the art (Garin-Chesa P, Old LJ, Rettig WJ: Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci USA 1990; 87:7235-7239) on five micrometer thickness fresh frozen sections. The antibodies L_AH_C, cF19 and hu IgG1 (at 1 μg/ml) were biotinylated according to the state of the art and were detected with streptavidin peroxidase complex. DAB was used as a substrate for the final reaction product. The sections were counterstained with Harris' hematoxylin and examined for antigen expression.

[0143] The normal tissues tested did not react with either L_AH_C or cF19 in the experiments (Table 1).

[0144] The normal human pancreas used as positive control showed L_AH_C and cF19 binding in a subset of endocrine cells in the islets of Langerhans as previously described for F19. In addition, binding of L_AH_C and cF19 was seen in the tumor stromal fibroblasts in the breast carcinoma sample.

[0145] Immunohistochemical analysis of normal tissues from mouse, rat, rabbit and cynomolgus failed to detect any binding of either L_AH_C or cF19, in the experiments performed.

Table 20

Binding of L_AH_C to tissue sections of non-human species, as determined by immunohistochemistry.					
Organ / Tissue typ		Mouse	Rat	Rabbit	Cynomolgus
Brain	-Cerebral cortex	-	-	-	
	-Cerebellum	-	-	-	-
Liver	-Hepatocytes	-	-	-	-
	-Portal triad	-	-	-	-
Lung	-Bronchi	-	-	-	-
	-Alveoli	-	-	-	-
Kidney	-Glomeruli	-	-	-	-
	-Tubular epithelium	-	-	-	-
Stomach	-Glandular epithelium				
	-Smooth muscle	-	-	-	-
Pancreas	-Exocrine acini	-	-	-	-
	-Endocrine islets	-	-	-	-
Intestine	-Glandular epithelium	-	-	-	-
	-Smooth muscle	-	-	-	-
Thymus -Lymphocytes		-	-	-	-
Skin	-Keratinocytes	-	-	-	-
	-Sweat glands	-	-	-	-
	-Hair follicles	-	-	-	-
Skeletal muscle		-	-	-	-
Heart		-	-	-	-
Spleen -Lymphocytes		-	-	-	-
Ovary	-Follicular epithelium	-	-	-	-
	-Stroma	-	-	-	-
Uterus	-Myometrium	-	-	-	-
	-Cervix uteri	-	-	-	-
Testis -Tubular epithelium		nt	nt	nt	-
Connective tissue		-	-	-	-

nt, not tested

Example 10: **Construction of cell lines producing chimeric and reshaped anti-FAP monoclonal antibodies**

[0146] The objective of this experiment was to demonstrate stable cell lines according to the invention expressing L_AH_C, L_AH_A, L_BH_B, L_BH_D, and cF19 in CHO DG44 cells. Stable cell lines transfected with humanized or chimeric F19 antibodies were produced and their identity was confirmed by PCR amplification of heavy and light variable regions using genomic DANN derived from each transfectant as template.

[0147] CHO DG44 cells maintained under serum-free conditions in SFM-II medium. Lipofectin and SFM-II serum-free medium were obtained from Gibco/BRL. Geneticin and all restriction enzymes were obtained from Boehringer Mannheim. Pfu polymerase was obtained from Stratagene.

[0148] DNA for transfections was purified from E. coli cells using QiaFilter Maxi Cartridges (Qiagen) as directed by the manufacturer. All DNA preparations were examined by restriction enzyme digestion. Sequences of L_AH_C variable regions in their respective vectors were confirmed using an ABI PRISM 310 Sequencer.

[0149] Further information regarding the vectors and DNA sequences employed is available in the prior examples.

Transfection of CHO DG44 cells

[0150] Cells in logarithmic growth were plated into 6 well plates containing 1 mL fresh SFM-II medium. Plasmids encoding heavy and light chains of humanized or chimeric F19 verions were cotransfected into CHO DG44 cells using liposomal transfection. Liposomes were prepared using 6 μl Lipofectin reagent and 0.5 μg of each vector (one for the desired heavy chain and one for the light) as described for LipofectAMINE transfections except that SFM-II medium was used to dilute all reagents. Twenty-four hours later, cells were diluted 1:10 into SFM-II medium containing 300 μg/mL Geneticin. After the initial phase of cell killing was over (10-14 days), the concentration of Geneticin was reduced to 200 mg/mL and methotrexate was added to a final concentration of 5 nM. Methotrexate concentrations were increased after 10-14 days to a final concentration of 20 nM.

PCR Amplification of transfectant DNA

[0151] 10^7 CHO DG44 cells were centrifuged in an Eppendorf microcentrifuge briefly at full speed, washed once with PBS, and pelleted once again. Genomic DNA was prepared by ethanol precipitation after SDS lysis and Proteinase K treatment of the cell pellets.

[0152] A mixture containing one of the following primer pairs, dNTPs, buffer, and Pfu polymerase was used to amplify either the heavy or light chain variable region using genomic DNA as template. The resulting PCR products were digested with the appropriate restriction enzyme and analyzed by agarose gel electrophoresis to confirm their identity.

Light chain primer set:

[0153]

5'-GAG ACA TTG TGA CCC AAT CTC C - 3' PKN 1690

5'- GAC AGT CAT AAA CTG CCA CAT CTT C - 3' PKN.1930.R

Heavy chain primer set:

[0154]

5'-TTG ACA CGC GTC TCG GGA AGC TT - 3' PG 5863

5'- GGC GCA GAG GAT CCA CTC ACC T - 3' PG 6332.R

[0155] The undigested heavy chain PCR product has a predicted size of 469 bp while the light chain PCR product has a predicted size of 286 bp. Verification of identity was determined by restriction enzyme digest with BstEII (heavy chain) or NlaIV (light chain).

[0156] CHO cell lines were transfected with L_AH_C, L_AH_A, L_BH_B, L_BH_D, as well as cF19. Geneticin-resistant cells were obtained and these cells were further selected for resistance to methotrexate. PCR amplification of the light and heavy chain DNA produced the expected bands and confirmed the identity of L_AH_C, L_AH_A and L_BH_D transfectants. The L_AH_C full length heavy chain PCR product was subcloned and resequenced in its entirety.

[0157] The cells described were maintained under serum-free conditions at all times and were not treated with animal-derived products such as trypsin.

[0158] Producer cell lines transfected with expressing monoclonal L_AH_C, L_AH_A, L_BH_B, L_BH_D and cF19 antibodies were produced. Their identities were confirmed using PCR amplification of both their heavy and light chain variable regions. The DNA sequence of the heavy chain variable region PCR products for L_AH_C-transfected cells was confirmed.

***Example* 11:Expression of antibody proteins in Chinese hamster ovary DG 44 cells and their purification**

[0159] The objective of this experiment was to express and purifiy of L_AH_C, L_AH_A, L_BH_B, and L_BH_D mAbs to enable their characterization. Other goals included the establishment of a quantitative ELISA to permit measurement of anti-

body concentrations in both crude media samples as well as purified Ig samples and determination of relative expression levels of various humanized F19 constructs using this assay.

[0160] Serum-free CHO DG44 cells and USP-grade methotrexate were obtained from the Biotechnical Production Unit of the Dr. Karl Thomae GmbH, Biberach, Germany; both products are also commercially available. Cells were maintained under serum-free conditions at all times. SFM-II serum-free medium was obtained from Gibco/BRL.

[0161] Protein A agarose was from Pierce Chemical (Indianapolis, IN, USA). Human IgG1 standards (Cat. No. I 3889), p-Nitrophenyl phosphate tablets (N 2640), bovine serum albumin (BSA) (A 7906), and goat anti-human kappa chain specific alkaline phosphatase-conjugated antibody (A 3813) were obtained from Sigma Chemical (St. Louis, MO, USA). Goat anti-human gamma-chain specific alkaline phosphatase-conjugated antibody was obtained from Jackson Immunoresearch Laboratories (through Stratech Scientific). Tris-buffered saline (TBS) consisted of 150 mM NaCl, 50 mM Tris, pH 7.5.

Cell culture conditions for antibody expression

[0162] Cells were cultured and L_AH_C-producing cells were maintained in T-175 flasks in SFM-II serum-free medium without agitation. The medium contained 200 μg/mL Geneticin and 20 nM methotrexate without antibiotics. Cells were passaged by dilution, were not adherent, and grew in small clusters. When the cells reached stationary phase, the medium was collected and centrifuged to remove cells and frozen at -20°C until needed.

Purification of L_AH_C

[0163] All purification steps were carried out at 4° C. A C10/10 column (Pharmacia Fine Chemicals) was packed with Protein A agarose (3 mL bed volume). The column was washed with TBS and preeluted once with 0.1 M Na citrate, pH 3.0 to insure that no loosely bound material remained on the column. The column was then immediately reequilibrated with TBS and stored at 4°C. Spent culture supernatants were thawed and centrifuged at 10,000 xg for 30 minutes prior to Protein A chromatography to remove debris and diluted with an equal volume of TBS. This material was loaded onto the Protein A column at 0.5 mL/min using a P-1 peristaltic pump (Pharmacia) and washed with TBS until the absorbance at 280 nm was undetectable. Elution of the anibody was initiated with 0.1 M Na citrate pH 3.0 at approximately 0.2 mL/min. The elution was monitored at 280 nm and one mL fractions of the eluted material were collected into tubes containing sufficient Tris base pH 9 to neutralize the citrate buffer. Protein-containing fractions were pooled and concentrated using an Amicon filtration apparatus with a YM-30 filter and dialyzed against PBS. The column was immediately regenerated with TBS. Protein dye-binding assays were performed with the BioRad (Hercules, California) protein determination kit, according to the manufacturer's instructions, using bovine serum albumin as a standard.

Human IgG (gamma immunoglobulin) ELISA

[0164] ELISA plates were coated overnight with 100 μL of goat anti-human gamma-chain specific alkaline phosphatase-conjugated antibody at 0.4 mg/mL in coating buffer at 4°C. Coating antibody was removed and plates were blocked with 2% BSA in PBS for 2 hours. All subsequent steps were performed at 37°C. Blocking buffer was replaced with antibody samples or human IgG1 standard diluted in dilution buffer, serially diluted in a 200mL volume, and incubated for one hour. Negative controls included dilution buffer and/or culture medium of nontransfected cells. Wells were washed and 100 μL of goat anti-human kappa chain specific alkaline phosphatase-conjugated antibody diluted 1:5000 was added and incubated for one hour. Wells were washed and 100 μL reaction buffer was added and incubated for 30 minutes. The reaction was stopped by addition of 1 M NaOH and absorbance read at 405 nm in an ELISA plate reader. Results were analyzed by four-parameter iterative curve fitting.

[0165] Amino acid analysis was performed according to methods available in the state of the art.

[0166] Monoclonal antibody L_AH_C was produced and purified to homogeneity using Protein A affinity chromatography. ELISA assays using human IgG1 as standard indicated L_AH_C recoveries exceeding 70%. The purity of the material was estimated to be >90% by SDS-polyacrylamide gel electrophoresis. Representative expression data and typical purification yields are shown in Table 21.

Table 21

Expression data and purification yields FAP antibody proteins in CHO cells			
Antibody	Expression levels in crude media samples (ELISA)	Purified antibody yields	Yield improvement [purified antibody]
H_CL_A	7 - 10 mg/L	~ 5 - 7 mg/L	500 - 700
H_AL_A	5 - 7 mg/mL	~ 3 - 4 mg/L	300 - 400
H_BL_B	0.5 - 1 mg/mL	~ 0.2 - 0.5 mg/L	20 - 50
H_DL_B	0.8 - 1.5 mg/mL	~ 0.3 - 0.8 mg/L	30 - 60
Chimeric F19	~ 0.02 mg/mL	< 0.01 mg/L	1
Representative expression data for each of the anti-FAP antibodies produced in this study are shown. Recoveries after Protein A agarose affinity chromatography were based on protein dye-binding measurements of the purified Ig using BSA as a standard.			

Example 12: **Binding of monoclonal antibody L_AH_C to isolated recombinant human FAP**

[0167] The objective of this study was to characterize binding of L_AH_C to isolated recombinant human FAP.

CD8-FAP ELISA

[0168] ELISA plates were coated overnight with 100 μL of mouse anti-rat antibody (Sigma Chemical R0761) at 1:2000 in coating buffer at 4 °C. Coating antibody was removed and plates were blocked with 2% BSA in PBS for one hour. All subsequent steps were performed at room temperature. Blocking buffer was replaced with 100 mL of 1 μg/mL rat anti-CD8 antibody (Pharmingen 01041D) and incubated for one hour. Plates were washed and 100 μL CD8-FAP culture supernatant (1:2 in PBS) was added and allowed to bind for one hour. Plates were washed and antibody samples were added (two-fold serial dilutions) in a 100 μL volume and incubated for one hour. Negative controls included human IgG and/or culture medium of nontransfected cells. Wells were washed and 100 μl of horse radish peroxidase (HRP) conjugated mouse anti-human IgG1 antibody (Zymed 05-3320) diluted 1:500 in dilution buffer were added and incubated for one hour. Wells were washed and 100 μL HRP substrate, (azino-bis (3-ethylbenzthiazoline 6-sulfonic) acid, Sigma Chemical A9941), were added and incubated for 60 minutes. The reaction was stopped by addition of 1 M NaOH and absorbance read at 405/490 nm in an ELISA plate reader. Results were analyzed by four parameter curve iterative curve fitting.

[0169] Alternatively, plates were coated directly with cF19. FAP (recombinant human FAP) was allowed to bind to these plates as above and biotinylated L_AH_C (~1 μg/mL) was then added. Antibody binding was detected with HRP-streptavidin conjugate as above.

Solubilization of membrane-bound human FAP

[0170] FAP-expressing 293FAP I/2 cells or control 293 cells were washed with PBS and lysed with 1% Triton X-114 in Tris-buffered saline. Nuclei and debris were removed by centrifugation at 10,000 xg. The supernatant was phase-partitioned (Estreicher A, Wohlend A, Belin D, Scheuning WD Vasalli JD. Characterization of the cellular binding site for the urokinase-type plasminogen activator. J Biol Chem 1989; 264:1180-1189) to enrich membrane proteins. The detergent phase was collected and diluted in buffer containing 1% Empigen BB (Calbiochem) to prevent reaggregation of the Triton X-114.

[0171] This material was subjected to Concanavalin A agarose chromatography (Rettig WJ, Garin-Chesa P, Healey JH, Su SL, Ozer HL, Schwab, M, Albino AP, Old LJ. Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin. Cancer Res 1993; 53:3327-3335).

Biotinylation of L_AH_C

[0172] L_AH_C (1-2 mg) was dialyzed against 50mM bicarbonate buffer and biotinylated with a ten-fold molar excess of

sulfosuccinimidyl-6-biotinamido hexanoate (NHS-LC biotin, Pierce Chemical, Rockford, Illinois, USA) for 2 hours at room temperature. Unreacted product was removed by repeated microdialysis in a microconcentrator.

Transient transfections

[0173] COS-7 cells (American Type Tissue Culture Collection, reference number CRL 1651) were cotransfected by electroporation with the heavy and light chain vectors encoding L_AH_C.

[0174] Anti-CD8 monoclonal antibody was immobilized onto microtiter plates. CD8-FAP from medium of insect cells infected with CD8-FAP baculovirus was allowed to bind to these plates. Spent medium from COS-7 cell cultures transiently transfected with two separate vectors encoding L_AH_C was serially diluted and added to the wells containing the immobilized CD8-FAP. L_AH_C bound to isolated immobilized CD8-FAP protein (Figure 35). Culture supernatants from mock-transfected COS-7 cells failed to demonstrate binding.

[0175] Recombinant membrane-bound FAP from detergent extracts of 293FAP I/2 cells or control extracts was serially diluted and immobilized via chimeric F19 monoclonal antibody bound to microtiter plates. Biotinylated L_AH_C bound recombinant human FAP immobilized with cF19 (Figure 36) in a concentration-dependent manner.

[0176] L_AH_C recognized isolated immobilized recombinant human FAP carrying the epitope for murine F19. L_AH_C bound to both CD8-FAP produced in insect cells, as well as FAP protein produced in 293FAP I/2 cells.

[0177] Culture supernatants from COS7 cells transfected with either heavy and light chain vectors encoding L_AH_C or without DNA (Control) were collected three days posttransfection. CD8-FAP was immobilized via an anti-CD8 antibody as described in the text. Serial dilutions of the COS7 supernatants were allowed to bind to the immobilized CD8-FAP and subsequently detected with an HRP-conjugated anti-human IgG1 antibody.

[0178] Detergent extracts of FAP-expressing 293FAP I/2 cells or control 293 cells were serially diluted and added to cF19-coated microtiter plates. Biotinylated L_AH_C was added and binding of biotinylated L_AH_C was detected with HRP-conjugated streptavidin.

Example 13: Characterization of HT-1080 fibrosarcoma cells and 293 human embryonic kidney cells transfected with cDNA for human FAP

[0179] Fibroblast activation protein (FAP) is a cell-surface, membrane-bound protein which carries the F19 epitope and is expressed on tumor stromal fibroblasts. Cell lines expressing recombinant FAP protein and matched controls lacking FAP were generated for the characterization of anti-FAP monoclonal antibodies.

[0180] Cells used were HT-1080 cells (reference number CCL 121) and 293 human embryonic kidney cells (reference number CRL 1573) were obtained from the American Type Culture Collection (Maryland, USA). Transfectam was obtained from Promega. Geneticin and all restriction enzymes were obtained from Boehringer Mannheim. DNA for transfections was purified from E. coli cells using QiaFilter Maxi Cartridges (Qiagen) as directed by the manufacturer. All DNA preparations were examined by restriction enzyme digestion. Vector sequences were confirmed using an ABI PRISM 310 Sequencer.

[0181] Further information regarding the vectors and DNA sequences employed has been described in Scanlan MJ, Raj BK, Calvo B, Garin-Chesa P, Sanz-Moncasi MP, Healey JH, Old LJ, Rettig WJ. Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci USA 1992; 89:10832-10836. The FAP cDNA sequence has been deposited in Genbank (accession number HS09287).

Cell culture and immunoassays

[0182] HT-1080 cells were transfected with 1 mg DNA using Transfectam according to the maufacturer's instructions. Human embryonic kidney 293 cells were transfected by calcium phosphate transfection (Brann MR; Buckley NJ; Jones SVP; Bonner TI.

[0183] Expression of cloned muscarinic receptor in A9 L cells. Mol Pharmacol 1987; 32:450-455) with 10 mg DNA. Twenty-four hours later, cells were diluted 1:10 into fresh medium containing 200 mg/mL Geneticin. Colonies were picked and examined by immunofluorescence for FAP expression as described in Rettig WJ; Garin-Chesa P; Beresford HR; Oettgen HF; Melamed MR; Old LJ. Cell-surface glycoproteins of human sarcomas: differential expression in normal and malignant tissues and cultured cells. Proc Natl Acad Sci USA 1988; 85:3110-3114.

[0184] Immunoprecipitations with cF19 were performed with metabolically labelled cells as described in Rettig WJ, Garin-Chesa P, Healey JH, Su SL, Ozer HL, Schwab, M, Albino AP, Old LJ. Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin. Cancer Res 1993; 53:3327-3335.

[0185] HT-1080 and 293 cells were tested for FAP antigen expression in immunofluorescence assays with anti-FAP

antibodies and were found to be antigen-negative. Transfection of these cells with FAP.38 vector resulted in the generation of Geneticin-resistant colonies. Isolated colonies were picked and analyzed by immunofluorescence for FAP expression. Two cell clones were identified, designated HT-1080FAP clone 33 and 293FAP I/2, which express cell surface-bound FAP protein, as recognized by cF19 antibody. Staining of nonpermeabilized HT-1080FAP clone 33 cells and 293FAP I/2 with cF19 antibody confirmed the cell surface localization of the FAP protein.

[0186] Immunoprecipitation of radiolabelled FAP protein with cF19 from extracts of ^{35}S-methionine labelled HT-1080FAP clone 33 cells or 293FAP I/2 cells resulted in the appearance of a 93 kilodalton band after autoradiography. This band is absent in immunoprecipitates of parental HT-1080 or 293 cell extracts.

[0187] Two stably transfected cell lines, HT-1080FAP clone 33 and 293FAP I/2, express FAP on the cell surface as determined in immunological assays with anti-FAP mAbs. Neither parental HT-1080 cells nor parental 293 cells express detectable levels of FAP.

Example 14: Generation and characterization of CD8-FAP fusion protein

[0188] A soluble form of human FAP (fibroblast activation protein) in the form of a CD8-FAP fusion protein was produced in insect cells for the characterization of L_AH_C containing the binding site for anti-FAP mAbs. Murine CD8 was chosen to permit secretion of the protein and to provide an additional epitope tag.

[0189] The cDNA encoding the extracellular domain of CD8, consisting of the first 189 amino acids of murine CD8, was linked to that of the extracellular domain of FAP (amino acids 27 to 760), essentially as described by Lane, et al. (Lane P, Brocker T, Hubele S, Padovan E, Lazavecchia A, McConnell. Soluble CD40 ligand can replace the normal T cell-derived CD40 ligand signal to B cells in T cell-dependent activation. J Exp Med 1993, 177:1209-1213) using standard PCR protocols. The authenticity of all clones was verified by DNA sequencing. The resulting DNA was inserted into the pVL1393 vector (Invitrogen) and transfection of Sf9 cells (Invitrogen) with this vector and amplification of the resulting recombinant baculovirus were performed as described (Baculovirus Expression Vectors. A Laboratory Manual. O'Reilly DR, Miller LK, Luckow VA, (Eds.), Oxford University Press: New York, 1994). The spent medium of High Five™ cells (Invitrogen) infected with recombinant CD8-FAP baculovirus for four days was collected and cleared by ultracentrifugation.

[0190] The CD8-FAP ELISA (enzyme-linked immunosorbent assay) has been described above (Example 12).

[0191] Insect cell cultures infected with CD8-FAP virus secreted a fusion protein into the medium which carries the F19 epitope and is recognized by an anti-FAP antibody (Figure 1). Neither the cell culture medium alone nor medium from insect cells infected with CD8-CD40L fusion protein bound anti-FAP antibody.

[0192] Soluble CD8-FAP protein carrying the F19 epitope was secreted into the medium of infected insected cell cultures. Culture supernatant from cells infected with a control construct did not contain antigen bearing the F19 epitope.

[0193] A soluble form of FAP, CD8-FAP, was produced in insect cells and CD8-FAP was shown to carry the epitope recognized by cF19.

[0194] Supernatants from insect cells infected with recombinant baculovirus encoding either CD8-FAP or CD8-CD40L fusion protein were collected four days postinfection. Cell culture medium without cells was used as an additional control (medium). Serial dilutions of these materials were added to anti-CD8 antibody-coated microtiter plates and allowed to bind. cF19 (1 mg/mL) was subsequently added and allowed to bind.

[0195] Bound cF19 was detected with horseradish peroxidase-conjugated anti-human antibody.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Boehringer Ingelheim International GmbH
(B) STREET: Rheinstrasse
(C) CITY: Ingelheim am Rhein
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(F) POSTAL CODE (ZIP): 55216
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(H) TELEFAX: ++49-6132-774377

(ii) TITLE OF INVENTION: FAP alpha-specific antibody with improved producibility

(iii) NUMBER OF SEQUENCES: 101

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA GAGGGCCACC 60

ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA ATCAAAAGAA CTACTTGGCC 120

TGGTATCAGC AGAAACCAGG ACAGCCACCC AAACTCCTCA TCTTTTGGGC TAGCACTAGG 180

GAATCTGGGG TACCTGATAG GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC 240

ATTAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATTACT GTCAGCAATA TTTTAGCTAT 300

CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA 339

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA GAGGGCCACC 60

ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA ATCAAAAGAA CTACTTGGCC 120

TGGTTCCAGC AGAAACCAGG ACAGCCACCC AAACTCCTCA TCTTTTGGGC TAGCACTAGG 180

GAATCTGGGG TACCTGATAG GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC 240

ATTAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATGACT GTCAACAATA TTTTAGCTAT 300

CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA 339

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Asp Cys Gln Gln
85 90 95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA GAGGGCCACC 60

ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA ATCAAAAGAA CTACTTGGCC 120

TGGTATCAGC AGAAACCAGG ACAGCCACCC AAACTCCTCA TCTATTGGGC TAGCACTAGG 180

GAATCTGGGG TACCTGATAG GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC 240

ATTAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATTACT GTCAGCAATA TTTTAGCTAT 300

CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA 339

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val

50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC 60

AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC 120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC 180

AACCAGAAGT TCAAGGGCCG GGCCACCTTG ACCGTAGGCA AGTCTGCCAG CACCGCCTAC 240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA 300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC 360

ACCGTCTCCT CA 372

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC 60

AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC 120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC 180

AACCAGAAGT TCAAGGGCCG GGCCACCTTG ACCGTAGGCA AGTCTGCCAG CACCGCCTAC 240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTTCTGCGC CAGAAGAAGA 300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC 360

ACCGTCTCCT CA 372

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC 60

AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC 120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC 180

AACCAGAAGT TCAAGGGCCG GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC 240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA 300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC 360

ACCGTCTCCT CA 372

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

```
                    85                  90                  95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

```
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC      60

AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC     120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC     180

AACCAGAAGT TCAAGGGCCG GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC     240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTTCTGCGC CAGAAGAAGA     300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC     360

ACCGTCTCCT CA                                                         372
```

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95
```

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC 60

AGCTGTAAAA CTAGTGGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC 120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC 180

AACCAGAAGT TCAAGGGCCG GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC 240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA 300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC 360

ACCGTCTCCT CA 372

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 220 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Phe Gly Thr Asp Phe Asn Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Asp Cys Gln Gln
85 90 95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 453 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

```
Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser
1               5                  10                  15

Val Lys Met Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr Thr
            20                  25                  30

Ile His Trp Val Arg Gln Ser His Gly Lys Ser Leu Glu Trp Ile Gly
        35                  40                  45

Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe Lys
    50                  55                  60

Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ser Ser Thr Ala Tyr Met
65                  70                  75                  80

Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
                85                  90                  95

Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
```

```
                340                 345                 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        355                 360                 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445

Leu Ser Pro Gly Lys
    450
```

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 321 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

```
CGTACTGTGG CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT      60

GGAACTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC CAAAGTACAG     120

TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG AGAGTGTCAC AGAGCAGGAC     180

AGCAAGGACA GCACCTACAG CCTCAGCAGC ACCCTGACGC TGAGCAAAGC AGACTACGAG     240

AAACACAAAG TCTACGCCTG CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG     300

AGCTTCAACA GGGGAGAGTG T                                               321
```

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30
```

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 990 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT CCTCCAAGAG CACCTCTGGG 60

GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG 120

TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA 180

GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC 240

TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC 300

AAATCTTGTG ACAAAACTCA CACATGCCCA CCGTGCCCAG CACCTGAACT CCTGGGGGGA 360

CCGTCAGTCT TCCTCTTCCC CCCAAAACCC AAGGACACCC TCATGATCTC CCGGACCCCT 420

GAGGTCACAT GCGTGGTGGT GGACGTGAGC CACGAAGACC CTGAGGTCAA GTTCAACTGG 480

TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC CGCGGGAGGA GCAGTACAAC 540

AGCACGTACC GGGTGGTCAG CGTCCTCACC GTCCTGCACC AGGACTGGCT GAATGGCAAG 600

GAGTACAAGT GCAAGGTCTC CAACAAAGCC CTCCCAGCCC CCATCGAGAA AACCATCTCC 660

AAAGCCAAAG GGCAGCCCCG AGAACCACAG GTGTACACCC TGCCCCCATC CCGGGAGGAG 720

ATGACCAAGA ACCAGGTCAG CCTGACCTGC CTGGTCAAAG GCTTCTATCC CAGCGACATC 780

GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAACT ACAAGACCAC GCCTCCCGTG 840

CTGGACTCCG ACGGCTCCTT CTTCCTCTAC AGCAAGCTCA CCGTGGACAA GAGCAGGTGG 900

CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG ATGCATGAGG CTCTGCACAA CCACTACACG 960

CAGAAGAGCC TCTCCCTGTC TCCGGGTAAA 990

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 330 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

AAGCTTGCCG CCACCATGGA TTCACAGGCC CAGGTTCTTA TGTTACTGCC GCTATGGGTA 60

TCTGGTACCT GTGGGGACAT TGTGATGTCA CAGTCTCCAT CCTCCCTAGC TGTGTCAGTT 120

GGAGAGAAGG TTACTATGAG CTGCAAGTCC AGTCAGAGCC TTTTATATAG TCGTAATCAA 180

AAGAACTACT TGGCCTGGTT CCAGCAGAAG CCAGGGCAGT CTCCTAAACT GCTGATTTTC 240

TGGGCATCCA CTAGGGAATC TGGGGTCCCT GATCGCTTCA CAGGCAGTGG ATTTGGGACG 300

GATTTCAATC TCACCATCAG CAGTGTGCAG GCTGAGGACC TGGCAGTTTA TGACTGTCAG 360

CAATATTTTA GCTATCCGCT CACGTTCGGT GCTGGGACCA AGCTGGAGCT GAAACGTGAG 420

TGGATCC 427

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Met Asp Ser Gln Ala Gln Val Leu Met Leu Leu Pro Leu Trp Val Ser
1 5 10 15

Gly Thr Cys Gly Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala
20 25 30

Val Ser Val Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu Tyr Ser Arg Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln
50 55 60

Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg
65 70 75 80

Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Phe Gly Thr Asp
85 90 95

Phe Asn Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr
100 105 110

Asp Cys Gln Gln Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr
115 120 125

Lys Leu Glu Leu Lys
130

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 457 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

AAGCTTGCCG CCACCATGGG ATGGAGCTGG GTCTTTCTCT TTCTCCTGTC AGGAACTGCA 60

GGTGTCCTCT CTGAGGTCCA GCTGCAACAG TCTGGACCTG AGCTGGTGAA GCCTGGGGCT 120

TCAGTAAAGA TGTCCTGCAA GACTTCTAGA TACACATTCA CTGAATACAC CATACACTGG 180

GTGAGACAGA GCCATGGAAA GAGCCTTGAG TGGATTGGAG GTATTAATCC TAACAATGGT 240

ATTCCTAACT ACAACCAGAA GTTCAAGGGC AGGGCCACAT TGACTGTAGG CAAGTCCTCC 300

AGCACCGCCT ACATGGAGCT CCGCAGCCTG ACATCTGAGG ATTCTGCGGT CTATTTCTGT 360

GCAAGAAGAA GAATCGCCTA TGGTTACGAC GAGGGCCATG CTATGGACTA CTGGGGTCAA 420

GGAACCTCAG TCACCGTCTC CTCAGGTGAG TGGATCC 457

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 143 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Met Gly Trp Ser Trp Val Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
20 25 30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser Arg Tyr Thr Phe
35 40 45

Thr Glu Tyr Thr Ile His Trp Val Arg Gln Ser His Gly Lys Ser Leu
50 55 60

Glu Trp Ile Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn
65 70 75 80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ser Ser
85 90 95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

Tyr Phe Cys Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His
115 120 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
130 135 140

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8068 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GAATTCCAGC ACACTGGCGG CCGTTACTAG TTATTAATAG TAATCAATTA CGGGGTCATT 60

AGTTCATAGC CCATATATGG AGTTCCGCGT TACATAACTT ACGGTAAATG GCCCGCCTGG 120

CTGACCGCCC AACGACCCCC GCCCATTGAC GTCAATAATG ACGTATGTTC CCATAGTAAC 180

GCCAATAGGG ACTTTCCATT GACGTCAATG GGTGGAGTAT TTACGGTAAA CTGCCCACTT 240

GGCAGTACAT CAAGTGTATC ATATGCCAAG TACGCCCCCT ATTGACGTCA ATGACGGTAA 300

ATGGCCCGCC TGGCATTATG CCCAGTACAT GACCTTATGG GACTTTCCTA CTTGGCAGTA 360

CATCTACGTA TTAGTCATCG CTATTACCAT GGTGATGCGG TTTTGGCAGT ACATCAATGG 420

GCGTGGATAG CGGTTTGACT CACGGGGATT TCCAAGTCTC CACCCCATTG ACGTCAATGG 480

GAGTTTGTTT TGGCACCAAA ATCAACGGGA CTTTCCAAAA TGTCGTAACA ACTCCGCCCC 540

ATTGACGCAA ATGGGCGGTA GGCGTGTACG GTGGGAGGTC TATATAAGCA GAGCTCGTTT 600

AGTGAACCGT CAGATCGCCT GGAGACGCCA TCCACGCTGT TTTGACCTCC ATAGAAGACA 660

CCGGGACCGA TCCAGCCTCC GCGGCCGGGA ACGGTGCATT GGAACGCGGA TTCCCCGTGC 720

CAAGAGTGAC GTAAGTACCG CCTATAGAGT CTATAGGCCC ACCCCCTTGG CTTCTTATGC 780

ATGCTATACT GTTTTTGGCT TGGGGTCTAT ACACCCCCGC TTCCTCATGT TATAGGTGAT 840

GGTATAGCTT AGCCTATAGG TGTGGGTTAT TGACCATTAT TGACCACTCC CCTATTGGTG 900

ACGATACTTT CCATTACTAA TCCATAACAT GGCTCTTTGC CACAACTCTC TTTATTGGCT 960

ATATGCCAAT ACACTGTCCT TCAGAGACTG ACACGGACTC TGTATTTTTA CAGGATGGGG 1020

TCTCATTTAT TATTTACAAA TTCACATATA CAACACCACC GTCCCCAGTG CCCGCAGTTT 1080

TTATTAAACA TAACGTGGGA TCTCCACGCG AATCTCGGGT ACGTGTTCCG GACATGGGCT 1140

CTTCTCCGGT AGCGGCGGAG CTTCTACATC CGAGCCCTGC TCCCATGCCT CCAGCGACTC 1200

ATGGTCGCTC GGCAGCTCCT TGCTCCTAAC AGTGGAGGCC AGACTTAGGC ACAGCACGAT 1260

GCCCACCACC ACCAGTGTGC CGCACAAGGC CGTGGCGGTA GGGTATGTGT CTGAAAATGA 1320

GCTCGGGGAG CGGGCTTGCA CCGCTGACGC ATTTGGAAGA CTTAAGGCAG CGGCAGAAGA 1380

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AGATGCAGGC AGCTGAGTTG TTGTGTTCTG ATAAGAGTCA GAGGTAACTC CCGTTGCGGT   1440
GCTGTTAACG GTGGAGGGCA GTGTAGTCTG AGCAGTACTC GTTGCTGCCG CGCGCGCCAC   1500
CAGACATAAT AGCTGACAGA CTAACAGACT GTTCCTTTCC ATGGGTCTTT TCTGCAGTCA   1560
CCGTCCTTGA CACGCGTCTC GGGAAGCTTG CCGCCACCAT GGATTCACAG GCCCAGGTTC   1620
TTATGTTACT GCCGCTATGG GTATCTGGTA CCTGTGGGGA CATTGTGATG TCACAGTCTC   1680
CATCCTCCCT AGCTGTGTCA GTTGGAGAGA AGGTTACTAT GAGCTGCAAG TCCAGTCAGA   1740
GCCTTTTATA TTCTAGAAAT CAAAAGAACT ACTTGGCCTG GTTCCAGCAG AAGCCAGGGC   1800
AGTCTCCTAA ACTGCTGATT TTCTGGGCAT CCACTAGGGA ATCTGGGGTC CCTGATCGCT   1860
TCACAGGCAG TGGATTTGGG ACGGATTTCA ATCTCACCAT CAGCAGTGTG CAGGCTGAGG   1920
ACCTGGCAGT TTATGACTGT CAGCAATATT TTAGCTATCC GCTCACGTTC GGTGCTGGGA   1980
CCAAGCTGGA GCTGAAACGT GAGTGGATCC ATCTGGGATA AGCATGCTGT TTTCTGTCTG   2040
TCCCTAACAT GCCCTGTGAT TATGCGCAAA CAACACACCC AAGGGCAGAA CTTTGTTACT   2100
TAAACACCAT CCTGTTTGCT TCTTTCCTCA GGAACTGTGG CTGCACCATC TGTCTTCATC   2160
TTCCCGCCAT CTGATGAGCA GTTGAAATCT GGAACTGCCT CTGTTGTGTG CCTGCTGAAT   2220
AACTTCTATC CCAGAGAGGC CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT   2280
AACTCCCAGG AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC   2340
ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC   2400
CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG TTAGAGGGAG   2460
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CCTTTTTCCA CAGGGGACCT ACCCCTATTG CGGTCCTCCA GCTCATCTTT CACCTCACCC   2580
CCCTCCTCCT CCTTGGCTTT AATTATGCTA ATGTTGGAGG AGAATGAATA AATAAAGTGA   2640
ATCTTTGCAC CTGTGGTGGA TCTAATAAAA GATATTTATT TTCATTAGAT ATGTGTGTTG   2700
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AGGCCAGAAT GACTCCAAGA GCTACAGGAA GGCAGGTCAG AGACCCCACT GGACAAACAG   2820
TGGCTGGACT CTGCACCATA ACACACAATC AACAGGGGAG TGAGCTGGAA ATTTGCTAGC   2880
GAATTCTTGA AGACGAAAGG GCCTCGTGAT ACGCCTATTT TTATAGGTTA ATGTCATGAT   2940
AATAATGGTT TCTTAGACGT CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT   3000
TTGTTTATTT TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA   3060
AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC GTGTCGCCCT   3120
TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT CACCCAGAAA CGCTGGTGAA   3180
AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT TACATCGAAC TGGATCTCAA   3240
CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT   3300
TAAAGTTCTG CTATGTGGCG CGGTATTATC CCGTGTTGAC GCCGGGCAAG AGCAACTCGG   3360
TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC TCACCAGTCA CAGAAAAGCA   3420
TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT GCCATAACCA TGAGTGATAA   3480
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CATACCAAAC GACGAGCGTG ACACCACGAT GCCTGCAGCA ATGGCAACAA CGTTGCGCAA 3660

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TGGTAAGCCC TCCCGTATCG TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA 3900

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CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT CATTTTTAAT TTAAAAGGAT 4020

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CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT 4140

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CAGGTAGGGC TGGCCTTGGG GGAGGGGGAG GCCAGAATGA CTCCAAGAGC TACAGGAAGG 7980

CAGGTCAGAG ACCCCACTGG ACAAACAGTG GCTGGACTCT GCACCATAAC ACACAATCAA 8040

CAGGGGAGTG AGCTGGAAAT TTGCTAGC 8068

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 239 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

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Asp Ser Gln Ala Gln Val Leu Met Leu Leu Pro Leu Trp Val Ser Gly
1               5                  10                  15

Thr Cys Gly Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val
            20                  25                  30

Ser Val Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Tyr Ser Arg Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln Lys
    50                  55                  60

Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Phe Gly Thr Asp Phe
                85                  90                  95

Asn Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Asp
            100                 105                 110

Cys Gln Gln Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys
        115                 120                 125

Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220
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Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7731 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

TTGAAGACGA AAGGGCCTCG TGATACGCCT ATTTTTATAG GTTAATGTCA TGATAATAAT 60

GGTTTCTTAG ACGTCAGGTG GCACTTTTCG GGGAAATGTG CGCGGAACCC CTATTTGTTT 120

ATTTTTCTAA ATACATTCAA ATATGTATCC GCTCATGAGA CAATAACCCT GATAAATGCT 180

TCAATAATAT TGAAAAAGGA AGAGTATGAG TATTCAACAT TTCCGTGTCG CCCTTATTCC 240

CTTTTTTGCG GCATTTTGCC TTCCTGTTTT TGCTCACCCA GAAACGCTGG TGAAAGTAAA 300

AGATGCTGAA GATCAGTTGG GTGCACGAGT GGGTTACATC GAACTGGATC TCAACAGCGG 360

TAAGATCCTT GAGAGTTTTC GCCCCGAAGA ACGTTTTCCA ATGATGAGCA CTTTTAAAGT 420

TCTGCTATGT GGCGCGGTAT TATCCCGTGT TGACGCCGGG CAAGAGCAAC TCGGTCGCCG 480

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GGCCAACTTA CTTCTGACAA CGATCGGAGG ACCGAAGGAG CTAACCGCTT TTTTGCACAA 660

CATGGGGGAT CATGTAACTC GCCTTGATCG TTGGGAACCG GAGCTGAATG AAGCCATACC 720

AAACGACGAG CGTGACACCA CGATGCCTGC AGCAATGGCA ACAACGTTGC GCAAACTATT 780

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GCCCTCCCGT ATCGTAGTTA TCTACACGAC GGGGAGTCAG GCAACTATGG ATGAACGAAA 1020

TAGACAGATC GCTGAGATAG GTGCCTCACT GATTAAGCAT TGGTAACTGT CAGACCAAGT 1080

TTACTCATAT ATACTTTAGA TTGATTTAAA ACTTCATTTT TAATTTAAAA GGATCTAGGT 1140

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TGTCCTTCTA GTGTAGCCGT AGTTAGGCCA CCACTTCAAG AACTCTGTAG CACCGCCTAC 1440

ATACCTCGCT CTGCTAATCC TGTTACCAGT GGCTGCTGCC AGTGGCGATA AGTCGTGTCT 1500

TACCGGGTTG GACTCAAGAC GATAGTTACC GGATAAGGCG CAGCGGTCGG GCTGAACGGG 1560

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GCTATTTACA CCACAAAGGA AAAAGCTGCA CTGCTATACA AGAAAATTAT GGAAAAATAT  3660
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GTAAATGAGT GCGACGGCCG GCAAGCCCCG CTCCCCGGGC TCTCGCGGTC GCACGAGGAT 7440

GCTTGGCACG TACCCCCTGT ACATACTTCC CGGGCGCCCA GCATGGAAAT AAAGCACCGG 7500

ATCTAATAAA AGATATTTAT TTTCATTAGA TATGTGTGTT GGTTTTTTGT GTGCAGTGCC 7560

TCTATCTGGA GGCCAGGTAG GGCTGGCCTT GGGGGAGGGG GAGGCCAGAA TGACTCCAAG 7620

AGCTACAGGA AGGCAGGTCA GAGACCCCAC TGGACAAACA GTGGCTGGAC TCTGCACCAT 7680

AACACACAAT CAACAGGGGA GTGAGCTGGA AATTTGCTAG CGAATTAATT C 7731

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 472 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

```
Met Gly Trp Ser Trp Val Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1               5                  10                  15

Val Leu Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser Arg Tyr Thr Phe
        35                  40                  45

Thr Glu Tyr Thr Ile His Trp Val Arg Gln Ser His Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Phe Cys Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His
        115                 120                 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
```

```
305                 310                 315                 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            340                 345                 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

```
GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA GAGGGCCACC      60

ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA ATCAAAAGAA CTACTTGGCC     120

TGGTATCAGC AGAAACCAGG ACAGCCACCC AAACTCCTCA TCTTTTGGGC TAGCACTAGG     180

GAATCTGGGG TACCTGATAG GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC     240

ATTAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATTACT GTCAGCAATA TTTTAGCTAT     300

CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA                            339
```

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                  10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                  10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Asp Cys Gln Gln
                85                  90                  95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                  10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Arg Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8068 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```
GAATTCCAGC ACACTGGCGG CCGTTACTAG TTATTAATAG TAATCAATTA CGGGGTCATT      60

AGTTCATAGC CCATATATGG AGTTCCGCGT TACATAACTT ACGGTAAATG GCCCGCCTGG     120

CTGACCGCCC AACGACCCCC GCCCATTGAC GTCAATAATG ACGTATGTTC CCATAGTAAC     180

GCCAATAGGG ACTTTCCATT GACGTCAATG GGTGGAGTAT TTACGGTAAA CTGCCCACTT     240

GGCAGTACAT CAAGTGTATC ATATGCCAAG TACGCCCCCT ATTGACGTCA ATGACGGTAA     300

ATGGCCCGCC TGGCATTATG CCCAGTACAT GACCTTATGG GACTTTCCTA CTTGGCAGTA     360

CATCTACGTA TTAGTCATCG CTATTACCAT GGTGATGCGG TTTTGGCAGT ACATCAATGG     420

GCGTGGATAG CGGTTTGACT CACGGGGATT TCCAAGTCTC CACCCCATTG ACGTCAATGG     480

GAGTTTGTTT TGGCACCAAA ATCAACGGGA CTTTCCAAAA TGTCGTAACA ACTCCGCCCC     540

ATTGACGCAA ATGGGCGGTA GGCGTGTACG GTGGGAGGTC TATATAAGCA GAGCTCGTTT     600
```

AGTGAACCGT CAGATCGCCT GGAGACGCCA TCCACGCTGT TTTGACCTCC ATAGAAGACA 660

CCGGGACCGA TCCAGCCTCC GCGGCCGGGA ACGGTGCATT GGAACGCGGA TTCCCCGTGC 720

CAAGAGTGAC GTAAGTACCG CCTATAGAGT CTATAGGCCC ACCCCCTTGG CTTCTTATGC 780

ATGCTATACT GTTTTTGGCT TGGGGTCTAT ACACCCCCGC TTCCTCATGT TATAGGTGAT 840

GGTATAGCTT AGCCTATAGG TGTGGGTTAT TGACCATTAT TGACCACTCC CCTATTGGTG 900

ACGATACTTT CCATTACTAA TCCATAACAT GGCTCTTTGC CACAACTCTC TTTATTGGCT 960

ATATGCCAAT ACACTGTCCT TCAGAGACTG ACACGGACTC TGTATTTTTA CAGGATGGGG 1020

TCTCATTTAT TATTTACAAA TTCACATATA CAACACCACC GTCCCCAGTG CCCGCAGTTT 1080

TTATTAAACA TAACGTGGGA TCTCCACGCG AATCTCGGGT ACGTGTTCCG GACATGGGCT 1140

CTTCTCCGGT AGCGGCGGAG CTTCTACATC CGAGCCCTGC TCCCATGCCT CCAGCGACTC 1200

ATGGTCGCTC GGCAGCTCCT TGCTCCTAAC AGTGGAGGCC AGACTTAGGC ACAGCACGAT 1260

GCCCACCACC ACCAGTGTGC CGCACAAGGC CGTGGCGGTA GGGTATGTGT CTGAAAATGA 1320

GCTCGGGGAG CGGGCTTGCA CCGCTGACGC ATTTGGAAGA CTTAAGGCAG CGGCAGAAGA 1380

AGATGCAGGC AGCTGAGTTG TTGTGTTCTG ATAAGAGTCA GAGGTAACTC CCGTTGCGGT 1440

GCTGTTAACG GTGGAGGGCA GTGTAGTCTG AGCAGTACTC GTTGCTGCCG CGCGCGCCAC 1500

CAGACATAAT AGCTGACAGA CTAACAGACT GTTCCTTTCC ATGGGTCTTT TCTGCAGTCA 1560

CCGTCCTTGA CACGCGTCTC GGGAAGCTTG CCGCCACCAT GGAGACAGAC ACACTCCTGC 1620

TATGGGTGCT GCTGCTCTGG GTTCCAGGTT CCTCCGGAGA CATTGTGATG ACCCAATCTC 1680

CAGACTCTTT GGCTGTGTCT CTAGGGGAGA GGGCCACCAT CAACTGCAAG TCCAGTCAGA 1740

GCCTTTTATA TTCTAGAAAT CAAAAGAACT ACTTGGCCTG GTATCAGCAG AAACCAGGAC 1800

AGCCACCCAA ACTCCTCATC TTTTGGGCTA GCACTAGGGA ATCTGGGGTA CCTGATAGGT 1860

TCAGTGGCAG TGGGTTTGGG ACAGACTTCA CCCTCACCAT TAGCAGCCTG CAGGCTGAAG 1920

ATGTGGCAGT TTATTACTGT CAGCAATATT TTAGCTATCC GCTCACGTTC GGACAAGGGA 1980

CCAAGGTGGA AATAAAACGT GAGTGGATCC ATCTGGGATA AGCATGCTGT TTTCTGTCTG 2040

TCCCTAACAT GCCCTGTGAT TATGCGCAAA CAACACACCC AAGGGCAGAA CTTTGTTACT 2100

TAAACACCAT CCTGTTTGCT TCTTTCCTCA GGAACTGTGG CTGCACCATC TGTCTTCATC 2160

TTCCCGCCAT CTGATGAGCA GTTGAAATCT GGAACTGCCT CTGTTGTGTG CCTGCTGAAT 2220

AACTTCTATC CCAGAGAGGC CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT 2280

AACTCCCAGG AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC 2340

ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC 2400

CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG TTAGAGGGAG 2460

AAGTGCCCCC ACCTGCTCCT CAGTTCCAGC CTGACCCCCT CCCATCCTTT GGCCTCTGAC 2520

CCTTTTTCCA CAGGGGACCT ACCCCTATTG CGGTCCTCCA GCTCATCTTT CACCTCACCC 2580

CCCTCCTCCT CCTTGGCTTT AATTATGCTA ATGTTGGAGG AGAATGAATA AATAAAGTGA 2640

ATCTTTGCAC CTGTGGTGGA TCTAATAAAA GATATTTATT TTCATTAGAT ATGTGTGTTG 2700

GTTTTTTGTG TGCAGTGCCT CTATCTGGAG GCCAGGTAGG GCTGGCCTTG GGGGAGGGGG 2760

AGGCCAGAAT GACTCCAAGA GCTACAGGAA GGCAGGTCAG AGACCCCACT GGACAAACAG 2820

TGGCTGGACT CTGCACCATA ACACACAATC AACAGGGGAG TGAGCTGGAA ATTTGCTAGC 2880

GAATTCTTGA AGACGAAAGG GCCTCGTGAT ACGCCTATTT TTATAGGTTA ATGTCATGAT 2940

AATAATGGTT TCTTAGACGT CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT 3000

TTGTTTATTT TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT AACCCTGATA 3060

AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT CAACATTTCC GTGTCGCCCT 3120

TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT CACCCAGAAA CGCTGGTGAA 3180

AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT TACATCGAAC TGGATCTCAA 3240

CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT 3300

TAAAGTTCTG CTATGTGGCG CGGTATTATC CCGTGTTGAC GCCGGGCAAG AGCAACTCGG 3360

TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC TCACCAGTCA CAGAAAAGCA 3420

TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT GCCATAACCA TGAGTGATAA 3480

CACTGCGGCC AACTTACTTC TGACAACGAT CGGAGGACCG AAGGAGCTAA CCGCTTTTTT 3540

GCACAACATG GGGGATCATG TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC 3600

CATACCAAAC GACGAGCGTG ACACCACGAT GCCTGCAGCA ATGGCAACAA CGTTGCGCAA 3660

ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA CAATTAATAG ACTGGATGGA 3720

GGCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT CCGGCTGGCT GGTTTATTGC 3780

TGATAAATCT GGAGCCGGTG AGCGTGGGTC TCGCGGTATC ATTGCAGCAC TGGGGCCAGA 3840

TGGTAAGCCC TCCCGTATCG TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA 3900

ACGAAATAGA CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTGGT AACTGTCAGA 3960

CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT CATTTTTAAT TTAAAAGGAT 4020

CTAGGTGAAG ATCCTTTTTG ATAATCTCAT GACCAAAATC CCTTAACGTG AGTTTTCGTT 4080

CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT 4140

GCGCGTAATC TGCTGCTTGC AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC 4200

GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG CGCAGATACC 4260

AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC TTCAAGAACT CTGTAGCACC 4320

GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT GCTGCCAGTG GCGATAAGTC 4380

GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT AAGGCGCAGC GGTCGGGCTG 4440

AACGGGGGGT TCGTGCACAC AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA 4500

CCTACAGCGT GAGCTATGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG CGGACAGGTA 4560

TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG GAGCTTCCAG GGGGAAACGC 4620

CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA CTTGAGCGTC GATTTTTGTG 4680

ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC AACGCGGCCT TTTTACGGTT 4740

CCTGGCCTTT TGCTGGCCTT TTGCTCACAT GTTCTTTCCT GCGTTATCCC CTGATTCTGT 4800

GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT CGCCGCAGCC GAACGACCGA 4860

GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCCTG ATGCGGTATT TTCTCCTTAC 4920

GCATCTGTGC GGTATTTCAC ACCGCATATG GTGCACTCTC AGTACAATCT GCTCTGATGC 4980

CGCATAGTTA AGCCAGTATA CACTCCGCTA TCGCTACGTG ACTGGGTCAT GGCTGCGCCC 5040

CGACACCCGC CAACACCCGC TGACGCGCCC TGACGGGCTT GTCTGCTCCC GGCATCCGCT 5100

TACAGACAAG CTGTGACCGT CTCCGGGAGC TGCATGTGTC AGAGGTTTTC ACCGTCATCA 5160

CCGAAACGCG CGAGGCAGCT GTGGAATGTG TGTCAGTTAG GGTGTGGAAA GTCCCCAGGC 5220

TCCCCAGCAG GCAGAAGTAT GCAAAGCATG CATCTCAATT AGTCAGCAAC CAGGCTCCCC 5280

AGCAGGCAGA AGTATGCAAA GCATGCATCT CAATTAGTCA GCAACCATAG TCCCGCCCCT 5340

AACTCCGCCC ATCCCGCCCC TAACTCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG 5400

ACTAATTTTT TTTATTTATG CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC TATTCCAGAA 5460

GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA AAGCTAGCTT CACGCTGCCG 5520

CAAGCACTCA GGGCGCAAGG GCTGCTAAAG GAAGCGGAAC ACGTAGAAAG CCAGTCCGCA 5580

GAAACGGTGC TGACCCCGGA TGAATGTCAG CTACTGGGCT ATCTGGACAA GGGAAAACGC 5640

AAGCGCAAAG AGAAAGCAGG TAGCTTGCAG TGGGCTTACA TGGCGATAGC TAGACTGGGC 5700

GGTTTTATGG ACAGCAAGCG AACCGGAATT GCCAGCTGGG GCGCCCTCTG GTAAGGTTGG 5760

GAAGCCCTGC AAAGTAAACT GGATGGCTTT CTTGCCGCCA AGGATCTGAT GGCGCAGGGG 5820

ATCAAGATCT GATCAAGAGA CAGGATGAGG ATCGTTTCGC ATGATTGAAC AAGATGGATT 5880

GCACGCAGGT TCTCCGGCCG CTTGGGTGGA GAGGCTATTC GGCTATGACT GGGCACAACA 5940

GACAATCGGC TGCTCTGATG CCGCCGTGTT CCGGCTGTCA GCGCAGGGGC GCCCGGTTCT 6000

TTTTGTCAAG ACCGACCTGT CCGGTGCCCT GAATGAACTG CAGGACGAGG CAGCGCGGCT 6060

ATCGTGGCTG GCCACGACGG GCGTTCCTTG CGCAGCTGTG CTCGACGTTG TCACTGAAGC 6120

GGGAAGGGAC TGGCTGCTAT TGGGCGAAGT GCCGGGGCAG GATCTCCTGT CATCTCACCT 6180

TGCTCCTGCC GAGAAAGTAT CCATCATGGC TGATGCAATG CGGCGGCTGC ATACGCTTGA 6240

TCCGGCTACC TGCCCATTCG ACCACCAAGC GAAACATCGC ATCGAGCGAG CACGTACTCG 6300

GATGGAAGCC GGTCTTGTCG ATCAGGATGA TCTGGACGAA GAGCATCAGG GGCTCGCGCC 6360

AGCCGAACTG TTCGCCAGGC TCAAGGCGCG CATGCCCGAC GGCGAGGATC TCGTCGTGAC 6420

CCATGGCGAT GCCTGCTTGC CGAATATCAT GGTGGAAAAT GGCCGCTTTT CTGGATTCAT 6480

CGACTGTGGC CGGCTGGGTG TGGCGGACCG CTATCAGGAC ATAGCGTTGG CTACCCGTGA 6540

TATTGCTGAA GAGCTTGGCG GCGAATGGGC TGACCGCTTC CTCGTGCTTT ACGGTATCGC 6600

CGCTCCCGAT TCGCAGCGCA TCGCCTTCTA TCGCCTTCTT GACGAGTTCT TCTGAGCGGG 6660

ACTCTGGGGT TCGAAATGAC CGACCAAGCG ACGCCCAACC TGCCATCACG AGATTTCGAT 6720

TCCACCGCCG CCTTCTATGA AAGGTTGGGC TTCGGAATCG TTTTCCGGGA CGCCGGCTGG 6780

ATGATCCTCC AGCGCGGGGA TCTCATGCTG GAGTTCTTCG CCCACCCCGG GCTCGATCCC 6840

CTCGCGAGTT GGTTCAGCTG CTGCCTGAGG CTGGACGACC TCGCGGAGTT CTACCGGCAG 6900

TGCAAATCCG TCGGCATCCA GGAAACCAGC AGCGGCTATC CGCGCATCCA TGCCCCCGAA 6960

CTGCAGGAGT GGGGAGGCAC GATGGCCGCT TTGGTCCCGG ATCTTTGTGA AGGAACCTTA 7020

CTTCTGTGGT GTGACATAAT TGGACAAACT ACCTACAGAG ATTTAAAGCT CTAAGGTAAA 7080

TATAAAATTT TTAAGTGTAT AATGTGTTAA ACTACTGATT CTAATTGTTT GTGTATTTTA 7140

GATTCCAACC TATGGAACTG ATGAATGGGA GCAGTGGTGG AATGCCTTTA ATGAGGAAAA 7200

CCTGTTTTGC TCAGAAGAAA TGCCATCTAG TGATGATGAG GCTACTGCTG ACTCTCAACA 7260

TTCTACTCCT CCAAAAAAGA AGAGAAAGGT AGAAGACCCC AAGGACTTTC CTTCAGAATT 7320

GCTAAGTTTT TTGAGTCATG CTGTGTTTAG TAATAGAACT CTTGCTTGCT TTGCTATTTA 7380

CACCACAAAG GAAAAAGCTG CACTGCTATA CAAGAAAATT ATGGAAAAAT ATTCTGTAAC 7440

CTTTATAAGT AGGCATAACA GTTATAATCA TAACATACTG TTTTTTCTTA CTCCACACAG 7500

GCATAGAGTG TCTGCTATTA ATAACTATGC TCAAAAATTG TGTACCTTTA GCTTTTTAAT 7560

TTGTAAAGGG GTTAATAAGG AATATTTGAT GTATAGTGCC TTGACTAGAG ATCATAATCA 7620

GCCATACCAC ATTTGTAGAG GTTTTACTTG CTTTAAAAAA CCTCCCACAC CTCCCCCTGA 7680

ACCTGAAACA TAAAATGAAT GCAATTGTTG TTGTTAACTT GTTTATTGCA GCTTATAATG 7740

GTTACAAATA AAGCAATAGC ATCACAAATT TCACAAATAA AGCATTTTTT TCACTGCATT 7800

CTAGTTGTGG TTTGTCCAAA CTCATCAATG TATCTTATCA TGTCTGGATC TAATAAAAGA 7860

TATTTATTTT CATTAGATAT GTGTGTTGGT TTTTTGTGTG CAGTGCCTCT ATCTGGAGGC 7920

CAGGTAGGGC TGGCCTTGGG GGAGGGGGAG GCCAGAATGA CTCCAAGAGC TACAGGAAGG 7980

CAGGTCAGAG ACCCCACTGG ACAAACAGTG GCTGGACTCT GCACCATAAC ACACAATCAA 8040

CAGGGGAGTG AGCTGGAAAT TTGCTAGC 8068

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 234 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Ser Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu Tyr Ser Arg Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg
65 70 75 80

Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp
85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
100 105 110

Tyr Cys Gln Gln Tyr Phe Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr
115 120 125

Lys Val Glu Ile Lys Arg Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 372 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC CGTGAAAGTC 60

AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA TACACTGGGT TAGACAGGCC 120

CCTGGCCAAA GGCTGGAGTG GATAGGAGGT ATTAATCCTA ACAATGGTAT TCCTAACTAC 180

AACCAGAAGT TCAAGGGCCG GGCCACCTTG ACCGTAGGCA AGTCTGCCAG CACCGCCTAC 240

ATGGAACTGT CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA 300

ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG AACCCTTGTC 360

ACCGTCTCCT CA 372

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His Ala Met Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7731 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

TTGAAGACGA AAGGGCCTCG TGATACGCCT ATTTTTATAG GTTAATGTCA TGATAATAAT 60

GGTTTCTTAG ACGTCAGGTG GCACTTTTCG GGGAAATGTG CGCGGAACCC CTATTTGTTT 120

ATTTTTCTAA ATACATTCAA ATATGTATCC GCTCATGAGA CAATAACCCT GATAAATGCT 180

TCAATAATAT TGAAAAAGGA AGAGTATGAG TATTCAACAT TTCCGTGTCG CCCTTATTCC 240

CTTTTTTGCG GCATTTTGCC TTCCTGTTTT TGCTCACCCA GAAACGCTGG TGAAAGTAAA 300

AGATGCTGAA GATCAGTTGG GTGCACGAGT GGGTTACATC GAACTGGATC TCAACAGCGG 360

TAAGATCCTT GAGAGTTTTC GCCCCGAAGA ACGTTTTCCA ATGATGAGCA CTTTTAAAGT 420

TCTGCTATGT GGCGCGGTAT TATCCCGTGT TGACGCCGGG CAAGAGCAAC TCGGTCGCCG 480

CATACACTAT TCTCAGAATG ACTTGGTTGA GTACTCACCA GTCACAGAAA AGCATCTTAC 540

GGATGGCATG ACAGTAAGAG AATTATGCAG TGCTGCCATA ACCATGAGTG ATAACACTGC 600

GGCCAACTTA CTTCTGACAA CGATCGGAGG ACCGAAGGAG CTAACCGCTT TTTTGCACAA 660

CATGGGGGAT CATGTAACTC GCCTTGATCG TTGGGAACCG GAGCTGAATG AAGCCATACC 720

AAACGACGAG CGTGACACCA CGATGCCTGC AGCAATGGCA ACAACGTTGC GCAAACTATT 780

AACTGGCGAA CTACTTACTC TAGCTTCCCG GCAACAATTA ATAGACTGGA TGGAGGCGGA 840

TAAAGTTGCA GGACCACTTC TGCGCTCGGC CCTTCCGGCT GGCTGGTTTA TTGCTGATAA 900

ATCTGGAGCC GGTGAGCGTG GGTCTCGCGG TATCATTGCA GCACTGGGGC CAGATGGTAA 960

GCCCTCCCGT ATCGTAGTTA TCTACACGAC GGGGAGTCAG GCAACTATGG ATGAACGAAA 1020

TAGACAGATC GCTGAGATAG GTGCCTCACT GATTAAGCAT TGGTAACTGT CAGACCAAGT 1080

TTACTCATAT ATACTTTAGA TTGATTTAAA ACTTCATTTT TAATTTAAAA GGATCTAGGT 1140

GAAGATCCTT TTTGATAATC TCATGACCAA AATCCCTTAA CGTGAGTTTT CGTTCCACTG 1200

AGCGTCAGAC CCCGTAGAAA AGATCAAAGG ATCTTCTTGA GATCCTTTTT TTCTGCGCGT 1260

AATCTGCTGC TTGCAAACAA AAAAACCACC GCTACCAGCG GTGGTTTGTT TGCCGGATCA 1320

AGAGCTACCA ACTCTTTTTC CGAAGGTAAC TGGCTTCAGC AGAGCGCAGA TACCAAATAC 1380

TGTCCTTCTA GTGTAGCCGT AGTTAGGCCA CCACTTCAAG AACTCTGTAG CACCGCCTAC 1440

ATACCTCGCT CTGCTAATCC TGTTACCAGT GGCTGCTGCC AGTGGCGATA AGTCGTGTCT 1500

TACCGGGTTG GACTCAAGAC GATAGTTACC GGATAAGGCG CAGCGGTCGG GCTGAACGGG 1560

GGGTTCGTGC ACACAGCCCA GCTTGGAGCG AACGACCTAC ACCGAACTGA GATACCTACA 1620

GCGTGAGCTA TGAGAAAGCG CCACGCTTCC CGAAGGGAGA AAGGCGGACA GGTATCCGGT 1680

AAGCGGCAGG GTCGGAACAG GAGAGCGCAC GAGGGAGCTT CCAGGGGGAA ACGCCTGGTA 1740

TCTTTATAGT CCTGTCGGGT TTCGCCACCT CTGACTTGAG CGTCGATTTT TGTGATGCTC 1800

GTCAGGGGGG CGGAGCCTAT GGAAAAACGC CAGCAACGCG GCCTTTTTAC GGTTCCTGGC 1860

CTTTTGCTGG CCTTTTGCTC ACATGTTCTT TCCTGCGTTA TCCCCTGATT CTGTGGATAA 1920

CCGTATTACC GCCTTTGAGT GAGCTGATAC CGCTCGCCGC AGCCGAACGA CCGAGCGCAG 1980

CGAGTCAGTG AGCGAGGAAG CGGAAGAGCG CCTGATGCGG TATTTTCTCC TTACGCATCT 2040

GTGCGGTATT TCACACCGCA TATGGTGCAC TCTCAGTACA ATCTGCTCTG ATGCCGCATA 2100

GTTAAGCCAG TATACACTCC GCTATCGCTA CGTGACTGGG TCATGGCTGC GCCCCGACAC 2160

CCGCCAACAC CCGCTGACGC GCCCTGACGG GCTTGTCTGC TCCCGGCATC CGCTTACAGA 2220

CAAGCTGTGA CCGTCTCCGG GAGCTGCATG TGTCAGAGGT TTTCACCGTC ATCACCGAAA 2280

CGCGCGAGGC AGCATGCATC TCAATTAGTC AGCAACCATA GTCCCGCCCC TAACTCCGCC 2340

CATCCCGCCC CTAACTCCGC CCAGTTCCGC CCATTCTCCG CCCCATGGCT GACTAATTTT 2400

TTTTATTTAT GCAGAGGCCG AGGCCGCCTC GGCCTCTGAG CTATTCCAGA AGTAGTGAGG 2460

AGGCTTTTTT GGAGGCCTAG GCTTTTGCAA AAAGCTAGCT TACAGCTCAG GGCTGCGATT 2520

TCGCGCCAAA CTTGACGGCA ATCCTAGCGT GAAGGCTGGT AGGATTTTAT CCCCGCTGCC 2580

ATCATGGTTC GACCATTGAA CTGCATCGTC GCCGTGTCCC AAAATATGGG GATTGGCAAG 2640

AACGGAGACC TACCCTGGCC TCCGCTCAGG AACGAGTTCA AGTACTTCCA AAGAATGACC 2700

ACAACCTCTT CAGTGGAAGG TAAACAGAAT CTGGTGATTA TGGGTAGGAA AACCTGGTTC 2760

TCCATTCCTG AGAAGAATCG ACCTTTAAAG GACAGAATTA ATATAGTTCT CAGTAGAGAA 2820

CTCAAAGAAC CACCACGAGG AGCTCATTTT CTTGCCAAAA GTTTGGATGA TGCCTTAAGA 2880

CTTATTGAAC AACCGGAATT GGCAAGTAAA GTAGACATGG TTTGGATAGT CGGAGGCAGT 2940

TCTGTTTACC AGGAAGCCAT GAATCAACCA GGCCACCTCA GACTCTTTGT GACAAGGATC 3000

ATGCAGGAAT TTGAAAGTGA CACGTTTTTC CCAGAAATTG ATTTGGGGAA ATATAAACTT 3060

CTCCCAGAAT ACCCAGGCGT CCTCTCTGAG GTCCAGGAGG AAAAAGGCAT CAAGTATAAG 3120

TTTGAAGTCT ACGAGAAGAA AGACTAACAG GAAGATGCTT TCAAGTTCTC TGCTCCCCTC 3180

CTAAAGCTAT GCATTTTTAT AAGACCATGG GACTTTTGCT GGCTTTAGAT CTTTGTGAAG 3240

GAACCTTACT TCTGTGGTGT GACATAATTG GACAAACTAC CTACAGAGAT TTAAAGCTCT 3300

AAGGTAAATA TAAAATTTTT AAGTGTATAA TGTGTTAAAC TACTGATTCT AATTGTTTGT 3360

GTATTTTAGA TTCCAACCTA TGGAACTGAT GAATGGGAGC AGTGGTGGAA TGCCTTTAAT 3420

GAGGAAAACC TGTTTTGCTC AGAAGAAATG CCATCTAGTG ATGATGAGGC TACTGCTGAC 3480

TCTCAACATT CTACTCCTCC AAAAAAGAAG AGAAAGGTAG AAGACCCCAA GGACTTTCCT 3540

TCAGAATTGC TAAGTTTTTT GAGTCATGCT GTGTTTAGTA ATAGAACTCT TGCTTGCTTT 3600

GCTATTTACA CCACAAAGGA AAAAGCTGCA CTGCTATACA AGAAAATTAT GGAAAAATAT 3660

TCTGTAACCT TTATAAGTAG GCATAACAGT TATAATCATA ACATACTGTT TTTTCTTACT 3720

CCACACAGGC ATAGAGTGTC TGCTATTAAT AACTATGCTC AAAAATTGTG TACCTTTAGC 3780

TTTTTAATTT GTAAAGGGGT TAATAAGGAA TATTTGATGT ATAGTGCCTT GACTAGAGAT 3840

CATAATCAGC CATACCACAT TTGTAGAGGT TTTACTTGCT TTAAAAAACC TCCCACACCT 3900

CCCCCTGAAC CTGAAACATA AAATGAATGC AATTGTTGTT GTTAACTTGT TTATTGCAGC 3960

TTATAATGGT TACAAATAAA GCAATAGCAT CACAAATTTC ACAAATAAAG CATTTTTTTC 4020

ACTGCATTCT AGTTGTGGTT TGTCCAAACT CATCAATGTA TCTTATCATG TCTGGATCTA 4080

ATAAAAGATA TTTATTTTCA TTAGATATGT GTGTTGGTTT TTTGTGTGCA GTGCCTCTAT 4140

CTGGAGGCCA GGTAGGGCTG GCCTTGGGGG AGGGGGAGGC CAGAATGACT CCAAGAGCTA 4200

CAGGAAGGCA GGTCAGAGAC CCCACTGGAC AAACAGTGGC TGGACTCTGC ACCATAACAC 4260

ACAATCAACA GGGGAGTGAG CTGGAAATTT GCTAGCGAAT TCCAGCACAC TGGCGGCCGT 4320

TACTAGTTAT TAATAGTAAT CAATTACGGG GTCATTAGTT CATAGCCCAT ATATGGAGTT 4380

CCGCGTTACA TAACTTACGG TAAATGGCCC GCCTGGCTGA CCGCCCAACG ACCCCCGCCC 4440

ATTGACGTCA ATAATGACGT ATGTTCCCAT AGTAACGCCA ATAGGGACTT TCCATTGACG 4500

TCAATGGGTG GAGTATTTAC GGTAAACTGC CCACTTGGCA GTACATCAAG TGTATCATAT 4560

GCCAAGTACG CCCCCTATTG ACGTCAATGA CGGTAAATGG CCCGCCTGGC ATTATGCCCA 4620

GTACATGACC TTATGGGACT TTCCTACTTG GCAGTACATC TACGTATTAG TCATCGCTAT 4680

TACCATGGTG ATGCGGTTTT GGCAGTACAT CAATGGGCGT GGATAGCGGT TTGACTCACG 4740

GGGATTTCCA AGTCTCCACC CCATTGACGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA 4800

ACGGGACTTT CCAAAATGTC GTAACAACTC CGCCCCATTG ACGCAAATGG GCGGTAGGCG 4860

TGTACGGTGG GAGGTCTATA TAAGCAGAGC TCGTTTAGTG AACCGTCAGA TCGCCTGGAG 4920

ACGCCATCCA CGCTGTTTTG ACCTCCATAG AAGACACCGG GACCGATCCA GCCTCCGCGG 4980

CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTGACGTAA GTACCGCCTA 5040

TAGAGTCTAT AGGCCCACCC CCTTGGCTTC TTATGCATGC TATACTGTTT TTGGCTTGGG 5100

GTCTATACAC CCCCGCTTCC TCATGTTATA GGTGATGGTA TAGCTTAGCC TATAGGTGTG 5160

GGTTATTGAC CATTATTGAC CACTCCCCTA TTGGTGACGA TACTTTCCAT TACTAATCCA 5220

TAACATGGCT CTTTGCCACA ACTCTCTTTA TTGGCTATAT GCCAATACAC TGTCCTTCAG 5280

AGACTGACAC GGACTCTGTA TTTTTACAGG ATGGGGTCTC ATTTATTATT TACAAATTCA 5340

CATATACAAC ACCACCGTCC CCAGTGCCCG CAGTTTTTAT TAAACATAAC GTGGGATCTC 5400

CACGCGAATC TCGGGTACGT GTTCCGGACA TGGGCTCTTC TCCGGTAGCG GCGGAGCTTC 5460

TACATCCGAG CCCTGCTCCC ATGCCTCCAG CGACTCATGG TCGCTCGGCA GCTCCTTGCT 5520

CCTAACAGTG GAGGCCAGAC TTAGGCACAG CACGATGCCC ACCACCACCA GTGTGCCGCA 5580

CAAGGCCGTG GCGGTAGGGT ATGTGTCTGA AAATGAGCTC GGGGAGCGGG CTTGCACCGC 5640

TGACGCATTT GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTTGT 5700

GTTCTGATAA GAGTCAGAGG TAACTCCCGT TGCGGTGCTG TTAACGGTGG AGGGCAGTGT 5760

AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT GACAGACTAA 5820

CAGACTGTTC CTTTCCATGG GTCTTTTCTG CAGTCACCGT CCTTGACACG CGTCTCGGGA 5880

AGCTTGCCGC CACCATGGAC TGGACCTGGC GCGTGTTTTG CCTGCTCGCC GTGGCTCCTG 5940

GGGCCCACAG CCAGGTGCAA CTGGTGCAGT CCGGCGCCGA AGTGAAGAAA CCCGGTGCTT 6000

CCGTGAAAGT CAGCTGTAAA ACTAGTAGAT ACACCTTCAC TGAATACACC ATACACTGGG 6060

TTAGACAGGC CCCTGGCCAA AGGCTGGAGT GGATAGGAGG TATTAATCCT AACAATGGTA 6120

TTCCTAACTA CAACCAGAAG TTCAAGGGCC GGGCCACCTT GACCGTAGGC AAGTCTGCCA 6180

GCACCGCCTA CATGGAACTG TCCAGCCTGC GCTCCGAGGA CACTGCAGTC TACTACTGCG 6240

CCAGAAGAAG AATCGCCTAT GGTTACGACG AGGGCCATGC TATGGACTAC TGGGGTCAAG 6300

GAACCCTTGT CACCGTCTCC TCAGGTGAGT GGATCCTCTG CGCCTGGGCC CAGCTCTGTC 6360

CCACACCGCG GTCACATGGC ACCACCTCTC TTGCAGCCTC CACCAAGGGC CCATCGGTCT 6420

TCCCCCTGGC ACCCTCCTCC AAGAGCACCT CTGGGGGCAC AGCGGCCCTG GGCTGCCTGG 6480

TCAAGGACTA CTTCCCCGAA CCGGTGACGG TGTCGTGGAA CTCAGGCGCC CTGACCAGCG 6540

GCGTGCACAC CTTCCCGGCT GTCCTACAGT CCTCAGGACT CTACTCCCTC AGCAGCGTGG 6600

TGACCGTGCC CTCCAGCAGC TTGGGCACCC AGACCTACAT CTGCAACGTG AATCACAAGC 6660

CCAGCAACAC CAAGGTGGAC AAGAAAGTTG AGCCCAAATC TTGTGACAAA ACTCACACAT 6720

GCCCACCGTG CCCAGCACCT GAACTCCTGG GGGGACCGTC AGTCTTCCTC TTCCCCCCAA 6780

AACCCAAGGA CACCCTCATG ATCTCCCGGA CCCCTGAGGT CACATGCGTG GTGGTGGACG 6840

TGAGCCACGA AGACCCTGAG GTCAAGTTCA ACTGGTACGT GGACGGCGTG GAGGTGCATA 6900

ATGCCAAGAC AAAGCCGCGG GAGGAGCAGT ACAACAGCAC GTACCGGGTG GTCAGCGTCC 6960

TCACCGTCCT GCACCAGGAC TGGCTGAATG GCAAGGAGTA CAAGTGCAAG GTCTCCAACA 7020

AAGCCCTCCC AGCCCCCATC GAGAAAACCA TCTCCAAAGC CAAAGGGCAG CCCCGAGAAC 7080

CACAGGTGTA CACCCTGCCC CCATCCCGGG AGGAGATGAC CAAGAACCAG GTCAGCCTGA 7140

CCTGCCTGGT CAAAGGCTTC TATCCCAGCG ACATCGCCGT GGAGTGGGAG AGCAATGGGC 7200

AGCCGGAGAA CAACTACAAG ACCACGCCTC CCGTGCTGGA CTCCGACGGC TCCTTCTTCC 7260

TCTACAGCAA GCTCACCGTG GACAAGAGCA GGTGGCAGCA GGGGAACGTC TTCTCATGCT 7320

CCGTGATGCA TGAGGCTCTG CACAACCACT ACACGCAGAA GAGCCTCTCC CTGTCTCCGG 7380

GTAAATGAGT GCGACGGCCG GCAAGCCCCG CTCCCCGGGC TCTCGCGGTC GCACGAGGAT 7440

GCTTGGCACG TACCCCCTGT ACATACTTCC CGGGCGCCCA GCATGGAAAT AAAGCACCGG 7500

ATCTAATAAA AGATATTTAT TTTCATTAGA TATGTGTGTT GGTTTTTTGT GTGCAGTGCC 7560

TCTATCTGGA GGCCAGGTAG GGCTGGCCTT GGGGGAGGGG GAGGCCAGAA TGACTCCAAG 7620

AGCTACAGGA AGGCAGGTCA GAGACCCCAC TGGACAAACA GTGGCTGGAC TCTGCACCAT 7680

AACACACAAT CAACAGGGGA GTGAGCTGGA AATTTGCTAG CGAATTAATT C 7731

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 472 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

```
Met Asp Trp Thr Trp Arg Val Phe Cys Leu Leu Ala Val Ala Pro Gly
1               5                  10                  15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Thr Ser Arg Tyr Thr Phe
        35                  40                  45

Thr Glu Tyr Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu
    50                  55                  60

Glu Trp Ile Gly Gly Ile Asn Pro Asn Asn Gly Ile Pro Asn Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Val Gly Lys Ser Ala Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Arg Arg Ile Ala Tyr Gly Tyr Asp Glu Gly His
        115                 120                 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300
```

```
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            340                 345                 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

ACCGTCTCCT CAGGTGAGTG GATCC 25

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

CCTCTCTTGC AGCC 14

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

CCTCTCTTGC AGCC 14

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Thr Val Ser Ser
1

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Ser Thr Lys Gly
1

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

ACCGTCTCCT CAGCCTCCAC CAAGGGC 27

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Thr Val Ser Ser Ser Thr Lys Gly
1 5

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

ACCGTCTCCT CAGCCTCCAC CAAGGGC 27

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Thr Val Ser Ser Ala Ser Thr Lys Gly
1 5

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

GAAATAAAAC GTGAGTGGAT CC 22

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

CTTCTTTCCT CAGGAACTGT GGCTGCA 27

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Thr Val Ala Ala
1

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

GAAATAAAAC GAACTGTGGC TGCA 24

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Glu Ile Lys Thr Val Ala Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

GAAATAAAAC GAACTGTGGC TGCA 24

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Glu Ile Lys Arg Thr Val Ala Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Met Asp Ser Gln Ala Gln Val Leu Met Leu Leu Leu Leu Trp Val Ser
1 5 10 15

Gly Thr Cys Gly
20

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Met Gly Trp Ser Trp Val Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly

1 5 10 15

Val Leu Ser

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

GCCGCCACC 9

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

CAGAAAGCTT GCCGCCACCA TGGATTCACA GGCCCAG 37

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Met Asp Ser Gln Ala Gln
1 5

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

CCGAGGATCC ACTCACGTTT CAGCTCCAGC TTGGT 35

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

CAGAAAGCTT GCCGCCACCA TGGGATGGAG CTGGGTC 37

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Met Gly Trp Ser Trp Val
1 5

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

CCGAGGATCC ACTCACCTGA GGAGACGGTG ACTGA 35

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

GTCATCACAA TGTCTCCGGA GGAACCTGGA ACCCAG 36

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

CTCCGGAGAC ATTGTGATGA CCCAATCTC 29

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

CTCCGGAGAC ATTGTGATGA CCCAATCTC 29

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

CAGTCAGAGC CTTTTATATT CTAGAAATCA AAAGAACTAC TTGGCCTGGT ATCAGCAGAA 60

ACCAGGACAG CC 72

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

ACCCCAGATT CCCTAGTGCT AGCCCAAAAG ATGAGGAGTT TGGG 44

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 67 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

TAGCACTAGG GAATCTGGGG TACCTGATAG GTTCAGTGGC AGTGGGTTTG GGACAGACTT 60

CACCCTC 67

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

GTCCCTTGTC CGAACGTGAG CGGATAGCTA AAATATTGCT GACAGTAATA AAC 53

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

GCTCACGTTC GGACAAGGGA CCAAGGTGGA AAT 33

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

CAGTCAGAGC CTTTTATATT CTAGAAATCA AAAGAACTAC TTGGCCTGGT TCCAGCAGAA 60

ACCAGGACAG CC 72

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

GTCCCTTGTC CGAACGTGAG CGGATAGCTA AAATATTGCT GACAGTCATA AACTGCC 57

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

CCCAAACTCC TCATCTATTG GGCTAGCACT AGGG 34

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

CCCTAGTGCT AGCCCAATAG ATGAGGAGTT TGGG 34

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

TACGCAAACC GCCTCTC 17

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

GAGTGCACCA TATGCGGT 18

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

AACAGCTATG ACCATG 16

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

GTTTTCCCAG TCACGAC 17

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

GTGTATTCAG TGAAGGTGTA TCTACTAGTT TTACAGCTGA CTTTCAC 47

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

TAGTAGATAC ACCTTCACTG AATACACCAT ACACTGGGTT AGACAGGCCC CTG 53

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

CCCTTGAACT TCTGGTTGTA GTTAGGAATA CCATTGTTAG GATTAATACC TCCTATCCAC 60

TCCAGCCTTT G 71

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

TAACTACAAC CAGAAGTTCA AGGGCCGGGC CACCTTGACC GTAGGCAAGT CTGCCAGCAC 60

CGCCTACATG G 71

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

GCATGGCCCT CGTCGTAACC ATAGGCGATT CTTCTTCTGG CGCAGTAGTA GACTGCAGTG 60

TCC 63

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

CTATGGTTAC GACGAGGGCC ATGCTATGGA CTACTGGGGT CAAGGAAC 48

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

TAACTACAAC CAGAAGTTCA AGGGCCGGGT CACCATCACC GTAGACACCT CTGCCAGCAC 60

CGCCTACATG G 71

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

GGACACTGCA GTCTACTTCT GCGCCAG 27

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

TACGCAAACC GCCTCTC 17

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

GAGTGCACCA TATGCGGT 18

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

CCTTTGGCCA GGGGCCTGTC TAACCCAGTG TATGGTGTAT TCAGTGAAGG TGCTATCCAC 60

TAGTTTCCAC TAGTTT 76

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

GTCACCGTCC TTGACACGCG TCTCGGGA 28

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

TTGGAGGAGG GTGCCAG 17

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

GAGACATTGT GACCCAATCT CC 22

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

GACAGTCATA AACTGCCACA TCTTC 25

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

TTGACACGCG TCTCGGGAAG CTT 23

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "PRIMER"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

GGCGCAGAGG ATCCACTCAC CT 22

Claims

1. An antibody protein having the complementary determining regions of the monoclonal antibody F19 (ATCC Accession No. HB 8269), said antibody protein specifically binding to fibroblast activation protein, characterized in that it has framework modifications resulting in the improved producibility in host cells as compared to a chimeric antibody having the variable regions of F19 and foreign constant regions.

2. An antibody protein characterised in that it has a variable light chain region and a variable heavy chain region according to claim 1, each joined to a human constant region.

3. The antibody protein of claim 2, wherein said human constant region of the light chain is a human kappa constant region.

4. The antibody protein of claim 2, wherein said human constant region of the heavy chain is a human gamma-1 constant region.

5. An antibody protein according to any one of claims 1 to 4, characterised in that its expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 10.

6. An antibody protein according to any one of claims 1 to 4, characterised in that its expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 20.

7. An antibody protein according to any one of claims 1 to 4, characterised in that its expression levels in crude media samples as determined by ELISA and/or purified antibody yields exceed the expression levels and/or purification yields of the chimeric antibodies without framework modifications by at least a factor of 100.

8. An antibody protein according to any one of claims 1 to 7, characterised in that it displays improved producibility in eucaryotic cells.

9. The antibody protein according to claim 8 wherein said eucaryotic cell is a chinese hamster ovary cell (CHO cell).

10. An antibody protein according to any one of claims 1 to 9, wherein the amino acid in Kabat position 87 of the light chain region is not asparagine.

11. The antibody protein of claim 10, wherein the amino acid in Kabat position 87 of the light chain region is selected from aromatic or aliphatic amino acids.

12. The antibody protein of claim 11, wherein said aromatic amino acid in Kabat position 87 of the light chain region is a tyrosine or phenylalanine.

13. The antibody protein according to any one of claims 1 to 12, wherein the amino acid in Kabat position 36 of the light chain region is selected from aromatic amino acids.

14. An antibody protein according to any one of claims 1 to 13 that contains the variable region of the light chain as set forth in SEQ ID NO: 2.

15. An antibody protein of claim 14 characterised in that the variable region of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1.

16. An antibody protein according to any one of claims 1 to 13 that contains the variable region of the light chain as set forth in SEQ ID NO: 6.

17. An antibody protein of claim 16 characterised in that the variable region of the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 5.

18. An antibody protein according to any one of claims 1 to 17 containing a variable region of the heavy chain as set forth in any one of SEQ ID NOs: 8, 10, 12, 14.

19. An antibody protein according to claim 18 characterised in that the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in SEQ ID NOs: 7, 9, 11, 13.

20. An antibody protein according to any one of claims 1 to 14 containing the variable region of the light chain as set forth in SEQ ID NO: 2 and the variable region of the heavy chain as set forth in SEQ ID NOs: 12.

21. The antibody protein of claim 20 characterised in that the variable region of the the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1 and the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 11.

23. An antibody protein according to any one of claims 1 to 13 containing the variable region of the light chain as set forth in SEQ ID NO: 2 and the variable region of the heavy chain as set forth in SEQ ID NOs: 8.

24. The antibody protein of claim 23 characterised in that the variable region of the the light chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 1 and the variable region of the heavy chain is encoded by a nucleotide sequence as set forth in SEQ ID NO: 7.

25. A nucleotide sequence encoding an antibody protein according to any one of claims 1 to 24.

26. A recombinant DNA vector that contains a nucleotide sequence of claim 25.

27. The recombinant DNA vector of claim 26, said vector being an expression vector.

28. A host cell carrying a vector according to claims 26 or 27.

29. The host cell of claim 28, wherein said host cell is a eucaryotic cell.

30. The host cell of claim 29, wherein said eucaryotic host cell is a mammalian cell.

31. The host cell of claim 30, wherein said host cell is a CHO or a COS cell.

32. A method of producing antibody proteins according to any one of claims 1 to 24, said method comprising the steps of:

(a) cultivating a host cell according to any one of claims 23 to 26 under conditions where said antibody protein is expressed by said host cell, and
(b) isolating said antibody protein.

33. The method of claim 32, wherein said host cell is a mammalian cell, preferably a CHO or COS cell.

34. The method of claim 32 or 33, wherein said host cell is cotransfected with two plasmids carrying the expression units for light and heavy chains respectively.

35. An antibody protein according to any one of claims 1 to 24, wherein said antibody protein is conjugated to a therapeutic agent.

36. The antibody protein of claim 35, wherein said therapeutic agent is a therapeutic agent selected from the group consisting of radioisotopes, toxins, toxoids, inflammatory agents and chemotherapeutic agents.

37. The antibody protein of claim 36, wherein said radioisotopes are β-emitting radioisotopes.

38. The antibody protein of claim 37, wherein said radioisotopes are selected from the group consisting of ^{186}Rhenium, ^{188}Rhenium, ^{131}Iodine and ^{90}Yttrium.

39. An antibody protein according to any one of claims 1 to 24, characterised in that it is labeled.

40. The antibody protein of claim 39, wherein said label is a detectable marker.

41. The antibody protein of claim 40, wherein the detectable marker is a detectable marker selected from the group consisting of enzymes, dyes, radioisotopes, and biotin.

42. An antibody protein according to any one of claims 1 to 24 conjugated to an imageable agent.

43. The antibody protein of claim 42, wherein the imageable agent is a radioisotope.

44. The antibody protein of claim 43, wherein said radioisotopes are gamma-emitting radioisotopes??.

45. The antibody protein of claim 44, wherein said radioisotopes is ^{125}I.

46. A pharmaceutical composition containing an antibody protein according to any one of claims 1 to 24 and a pharmaceutically acceptable carrier useful for treating tumors, wherein said tumors are associated with activated stromal fibroblasts.

47. A pharmaceutical composition containing an antibody protein according to any one of claims 35 to 38 and a pharmaceutically acceptable carrier useful for treating tumors, wherein said tumors are associated with activated stromal fibroblasts.

48. A pharmaceutical composition containing an antibody protein according to any one of claims 42 to 45 and a pharmaceutically acceptable carrier useful for imaging the presence of activated stromal fibroblasts in a healing wound, inflamed skin or a tumor, in a human patient.

49. The pharmaceutical composition of claims 46 to 48, wherein said tumors are tumors selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain.

50. Use of an antibody protein according to anyone of claims 1 to 24 for the treatment of cancer.

51. Use of an antibody protein according to anyone of claims 35 to 38 for the treatment of cancer.

52. Use of an antibody protein according to anyone of claims 42 to 45 for imaging activated activated stromal fibroblasts.

53. Use of an antibody protein according to anyone of claims 39 to 41 for detecting the presence of activated stromal fibroblasts in a sample.

54. A method of treating tumors, wherein the tumor is associated with activated stromal fibroblasts capable of specifically forming a complex with antibody proteins according to any one of claims 1 to 24 or 35 to 38, which comprises contacting the tumor with an amount of said antibody proteins effective to treat the tumor.

55. The method of claim 54, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain.

56. The method of claim 54, wherein the contacting is effected in vitro.

57. The method of claim 54, wherein the contacting is effected in vivo.

58. A method of detecting the presence of activated stromal fibroblasts in wound healing, inflammation or a tumor, characterised in that

(a) a sample, possibly containing activated stromal fibroblasts, is contacted with an antibody protein according to any one of claims 1 to 24 or 39 to 41 under conditions suitable for the formation of a complex between said antibody and antigen,
(b) detecting the presence of said complex, thereby detecting the presence of activated stromal fibroblasts in wound healing, inflammation or a tumor.

59. The method of claim 58, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain.

60. The method of claim 58 or 59, wherein the antibody protein is a protein according to any one of claims 39 to 41.

61. A method of imaging the presence of activated stromal fibroblasts in a healing wound, inflamed skin or a tumor, in a human patient, characterised in that

(a) an antibody protein according to any one of claims 1 to 24 conjugated to an imageable agent is administered to a human patient under conditions suitable for the formation of an antibody-antigen complex,
(b) imaging any complex formed in this manner,
(c) thereby imaging the presence of activated stromal fibroblasts in a human patient.

62. The method of claim 61, wherein the tumor is a tumor having cancer cells selected from the cancer group consisting of colorectal cancers, non-small cell lung cancers, breast cancers, head and neck cancer, ovarian cancers, lung cancers, bladder cancers, pancreatic cancers and metastatic cancers of the brain.

63. A method of detecting tumor-stroma, characterised in that

(a) a suitable sample is contacted with an antibody protein according to any one of claims 1 to 24, under conditions suitable for the formation of an antibody-antigen complex,
(b) detecting the presence of any complex so formed,
(c) relating the presence of said complex to the presence of tumor-stroma.

64. The method of claim 62, wherein said antibody is labelled with a detectable marker.

65. A method of imaging tumor-stroma in a human patient, which comprises

(a) adminstering to the patient an antibody protein according to any one of claims 42 to 45, under conditions suitable for the formation of an antibody-antigen complex,
(b) imaging any complex so formed, and thereby imaging the presence of tumor-stroma in a human patient.

Fig. 1

```
1           11          21          31          41
GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA
51          61          71          81          91
GAGGGCCACC ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA
101         111         121         131         141
ATCAAAAGAA CTACTTGGCC TGGTATCAGC AGAAACCAGG ACAGCCACCC
151         161         171         181         191
AAACTCCTCA TCTTTTGGGC TAGCACTAGG GAATCTGGGG TACCTGATAG
201         211         221         231         241
GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC ATTAGCAGCC
251         261         271         281         291
TGCAGGCTGA AGATGTGGCA GTTTATTACT GTCAGCAATA TTTTAGCTAT
301         311         321         331    339
CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA
```

Fig. 2

```
1           11          21          31          41
DIVMTQSPDS LAVSLGERAT INCKSSQSLL YSRNQKNYLA WYQQKPGQPP
51          61          71          81          91
KLLIFWASTR ESGVPDRFSG SGFGTDFTLT ISSLQAEDVA VYYCQQYFSY
101         111
PLTFGQGTKV EIK
```

Fig. 3

```
1           11          21          31          41
GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA
51          61          71          81          91
GAGGGCCACC ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA
101         111         121         131         141
ATCAAAAGAA CTACTTGGCC TGGTTCCAGC AGAAACCAGG ACAGCCACCC
151         161         171         181         191
AAACTCCTCA TCTTTTGGGC TAGCACTAGG GAATCTGGGG TACCTGATAG
201         211         221         231         241
GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC ATTAGCAGCC
251         261         271         281         291
TGCAGGCTGA AGATGTGGCA GTTTATGACT GTCAACAATA TTTTAGCTAT
301         311         321         331    339
CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA
```

Fig. 4

```
1           11          21          31          41
DIVMTQSPDS LAVSLGERAT INCKSSQSLL YSRNQKNYLA WFQQKPGQPP
51          61          71          81          91
KLLIFWASTR ESGVPDRFSG SGFGTDFTLT ISSLQAEDVA VYDCQQYFSY
101         111
PLTFGQGTKV EIK
```

Fig. 5

```
1           11          21          31          41
GACATTGTGA TGACCCAATC TCCAGACTCT TTGGCTGTGT CTCTAGGGGA
51          61          71          81          91
GAGGGCCACC ATCAACTGCA AGTCCAGTCA GAGCCTTTTA TATTCTAGAA
101         111         121         131         141
ATCAAAAGAA CTACTTGGCC TGGTATCAGC AGAAACCAGG ACAGCCACCC
151         161         171         181         191
AAACTCCTCA TCTATTGGGC TAGCACTAGG GAATCTGGGG TACCTGATAG
201         211         221         231         241
GTTCAGTGGC AGTGGGTTTG GGACAGACTT CACCCTCACC ATTAGCAGCC
251         261         271         281         291
TGCAGGCTGA AGATGTGGCA GTTTATTACT GTCAGCAATA TTTTAGCTAT
301         311         321         331   339
CCGCTCACGT TCGGACAAGG GACCAAGGTG GAAATAAAA
```

Fig. 6

```
1           11          21          31          41
DIVMTQSPDS LAVSLGERAT INCKSSQSLL YSRNQKNYLA WYQQKPGQPP
51          61          71          81          91
KLLIYWASTR ESGVPDRFSG SGFGTDFTLT ISSLQAEDVA VYYCQQYFSY
101         111
PLTFGQGTKV EIK
```

Fig. 7

```
1
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC
51
CGTGAAAGTC AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA
101
TACACTGGGT TAGACAGGCC CCTGGCCAAA GGCTGGAGTG GATAGGAGGT
151
ATTAATCCTA ACAATGGTAT TCCTAACTAC AACCAGAAGT TCAAGGGCCG
201
GGCCACCTTG ACCGTAGGCA AGTCTGCCAG CACCGCCTAC ATGGAACTGT
251
CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA
301
ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG
351                   372
AACCCTTGTC ACCGTCTCCT CA
```

Fig. 8

```
1           11          21          31          41
QVQLVQSGAE VKKPGASVKV SCKTSRYTFT EYTIHWVRQA PGQRLEWIGG
51          61          71          81          91
INPNNGIPNY NQKFKGRATL TVGKSASTAY MELSSLRSED TAVYYCARRR
101         111         121-124
IAYGYDEGHA MDYWGQGTLV TVSS
```

Fig. 9

```
1
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC
51
CGTGAAAGTC AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA
101
TACACTGGGT TAGACAGGCC CCTGGCCAAA GGCTGGAGTG GATAGGAGGT
151
ATTAATCCTA ACAATGGTAT TCCTAACTAC AACCAGAAGT TCAAGGGCCG
201
GGCCACCTTG ACCGTAGGCA AGTCTGCCAG CACCGCCTAC ATGGAACTGT
251
CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTTCTGCGC CAGAAGAAGA
301
ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG
351                   372
AACCCTTGTC ACCGTCTCCT CA
```

Fig. 10

```
1           11          21          31          41
QVQLVQSGAE VKKPGASVKV SCKTSRYTFT EYTIHWVRQA PGQRLEWIGG
51          61          71          81          91
INPNNGIPNY NQKFKGRATL TVGKSASTAY MELSSLRSED TAVYFCARRR
101         111         121-124
IAYGYDEGHA MDYWGQGTLV TVSS
```

Fig. 11

```
1
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC
51
CGTGAAAGTC AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA
101
TACACTGGGT TAGACAGGCC CCTGGCCAAA GGCTGGAGTG GATAGGAGGT
151
ATTAATCCTA ACAATGGTAT TCCTAACTAC AACCAGAAGT TCAAGGGCCG
201
GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC ATGGAACTGT
251
CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA
301
ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG
351                 372
AACCCTTGTC ACCGTCTCCT CA
```

Fig. 12

```
1           11          21          31          41
QVQLVQSGAE VKKPGASVKV SCKTSRYTFT EYTIHWVRQA PGQRLEWIGG
51          61          71          81          91
INPNNGIPNY NQKFKGRVTI TVDTSASTAY MELSSLRSED TAVYYCARRR
101         111         121-124
IAYGYDEGHA MDYWGQGTLV TVSS
```

Fig. 13

```
1
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC
51
CGTGAAAGTC AGCTGTAAAA CTAGTAGATA CACCTTCACT GAATACACCA
101
TACACTGGGT TAGACAGGCC CCTGGCCAAA GGCTGGAGTG GATAGGAGGT
151
ATTAATCCTA ACAATGGTAT TCCTAACTAC AACCAGAAGT TCAAGGGCCG
201
GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC ATGGAACTGT
251
CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTTCTGCGC CAGAAGAAGA
301
ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG
351                     372
AACCCTTGTC ACCGTCTCCT CA
```

Fig. 14

```
1           11          21          31          41
QVQLVQSGAE VKKPGASVKV SCKTSRYTFT EYTIHWVRQA PGQRLEWIGG
51          61          71          81          91
INPNNGIPNY NQKFKGRVTI TVDTSASTAY MELSSLRSED TAVYFCARRR
101         111         121-124
IAYGYDEGHA MDYWGQGTLV TVSS
```

Fig. 15

```
1
CAGGTGCAAC TAGTGCAGTC CGGCGCCGAA GTGAAGAAAC CCGGTGCTTC
51
CGTGAAAGTC AGCTGTAAAA CTAGTGGATA CACCTTCACT GAATACACCA
101
TACACTGGGT TAGACAGGCC CCTGGCCAAA GGCTGGAGTG GATAGGAGGT
151
ATTAATCCTA ACAATGGTAT TCCTAACTAC AACCAGAAGT TCAAGGGCCG
201
GGTCACCATC ACCGTAGACA CCTCTGCCAG CACCGCCTAC ATGGAACTGT
251
CCAGCCTGCG CTCCGAGGAC ACTGCAGTCT ACTACTGCGC CAGAAGAAGA
301
ATCGCCTATG GTTACGACGA GGGCCATGCT ATGGACTACT GGGGTCAAGG
351                     372
AACCCTTGTC ACCGTCTCCT CA
```

Fig. 16

```
1           11          21          31          41
QVQLVQSGAE VKKPGASVKV SCKTSGYTFT EYTIHWVRQA PGQRLEWIGG
51          61          71          81          91
INPNNGIPNY NQKFKGRVTI TVDTSASTAY MELSSLRSED TAVYYCARRR
101         111         121-124
IAYGYDEGHA MDYWGQGTLV TVSS
```

Fig. 17

```
1
DIVMSQSPSS LAVSVGEKVT MSCKSSQSLL YSRNQKNYLA WFQQKPGQSP
51
KLLIFWASTR ESGVPDRFTG SGFGTDFNLT ISSVQAEDLA VYDCQQYFSY
101
PLTFGAGTKL ELKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA
151
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC
201
EVTHQGLSSP VTKSFNRGEC
```

Fig. 18

```
1
VQLQQSGPEL VKPGASVKMS CKTSRYTFTE YTIHWVRQSH GKSLEWIGGI
51
NPNNGIPNYN QKFKGRATLT VGKSSSTAYM ELRSLTSEDS AVYFCARRRI
101
AYGYDEGHAM DYWGQGTSVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC
151
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG
201
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP
251
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
301
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
351
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT
401
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
451
PGK
```

Fig. 19

```
340         350         360         370         380
CGTACTGTGG CTGCACCATC TGTCTTCATC TTCCCGCCAT CTGATGAGCA
390         400         410         420         430
GTTGAAATCT GGAACTGCCT CTGTTGTGTG CCTGCTGAAT AACTTCTATC
440         450         460         470         480
CCAGAGAGGC CAAAGTACAG TGGAAGGTGG ATAACGCCCT CCAATCGGGT
490         500         510         520         530
AACTCCCAGG AGAGTGTCAC AGAGCAGGAC AGCAAGGACA GCACCTACAG
540         550         560         570         580
CCTCAGCAGC ACCCTGACGC TGAGCAAAGC AGACTACGAG AAACACAAAG
590         600         610         620         630
TCTACGCCTG CGAAGTCACC CATCAGGGCC TGAGCTCGCC CGTCACAAAG
640         650         660
AGCTTCAACA GGGGAGAGTGT
```

Fig. 20

```
114         124         134         144         154
RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG
164         174         184         194         204
NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK
214-220
SFNRGEC
```

Fig. 21

```
373
GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT CCTCCAAGAG
423
CACCTCTGGG GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC
473
CCGAACCGGT GACGGTGTCG TGGAACTCAG GCGCCCTGAC CAGCGGCGTG
523
CACACCTTCC CGGCTGTCCT ACAGTCCTCA GGACTCTACT CCCTCAGCAG
573
CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC TACATCTGCA
623
ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGTTGAGCCC
673
AAATCTTGTG ACAAAACTCA CACATGCCCA CCGTGCCCAG CACCTGAACT
723
CCTGGGGGGA CCGTCAGTCT TCCTCTTCCC CCCAAAACCC AAGGACACCC
773
TCATGATCTC CCGGACCCCT GAGGTCACAT GCGTGGTGGT GGACGTGAGC
823
CACGAAGACC CTGAGGTCAA GTTCAACTGG TACGTGGACG GCGTGGAGGT
873
GCATAATGCC AAGACAAAGC CGCGGGAGGA GCAGTACAAC AGCACGTACC
923
GGGTGGTCAG CGTCCTCACC GTCCTGCACC AGGACTGGCT GAATGGCAAG
973
GAGTACAAGT GCAAGGTCTC CAACAAAGCC CTCCCAGCCC CCATCGAGAA
1023
AACCATCTCC AAAGCCAAAG GGCAGCCCCG AGAACCACAG GTGTACACCC
1073
TGCCCCCATC CCGGGAGGAG ATGACCAAGA ACCAGGTCAG CCTGACCTGC
1123
CTGGTCAAAG GCTTCTATCC CAGCGACATC GCCGTGGAGT GGGAGAGCAA
1173
TGGGCAGCCG GAGAACAACT ACAAGACCAC GCCTCCCGTG CTGGACTCCG
1223
ACGGCTCCTT CTTCCTCTAC AGCAAGCTCA CCGTGGACAA GAGCAGGTGG
1273
CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG ATGCATGAGG CTCTGCACAA
1323                                        1362
CCACTACACG CAGAAGAGCC TCTCCCTGTC TCCGGGTAAA
```

Fig. 22

```
125
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV
175
HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP
225
KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS
275
HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK
325
EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC
375
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW
425                          454
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
```

Fig. 23A

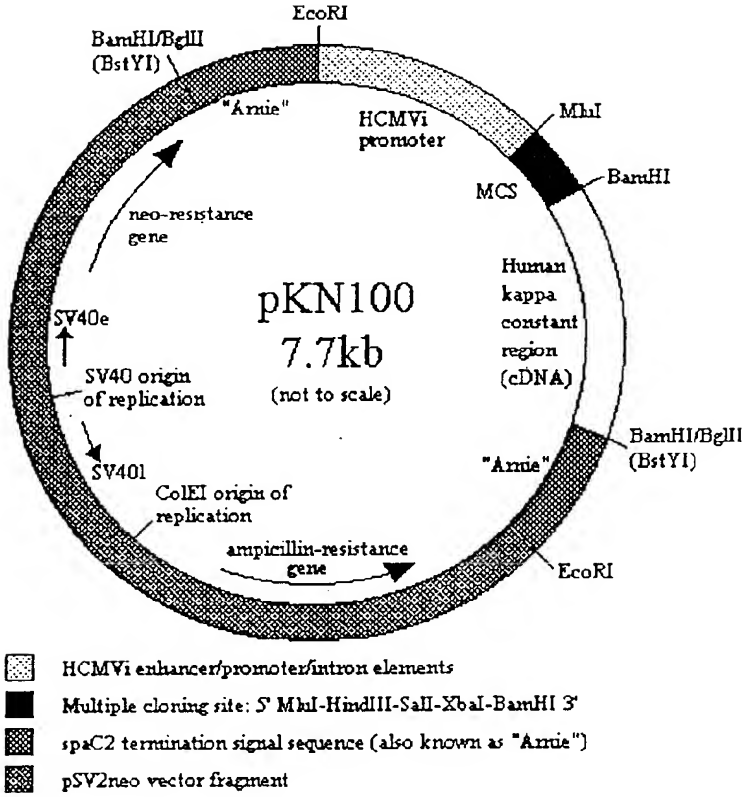

Fig. 23B

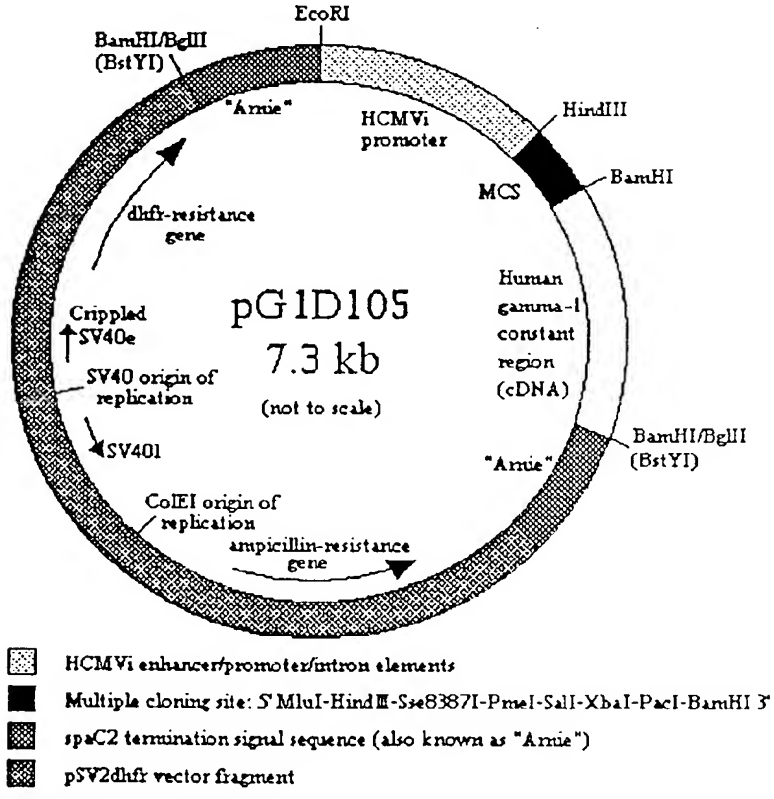

Fig. 24

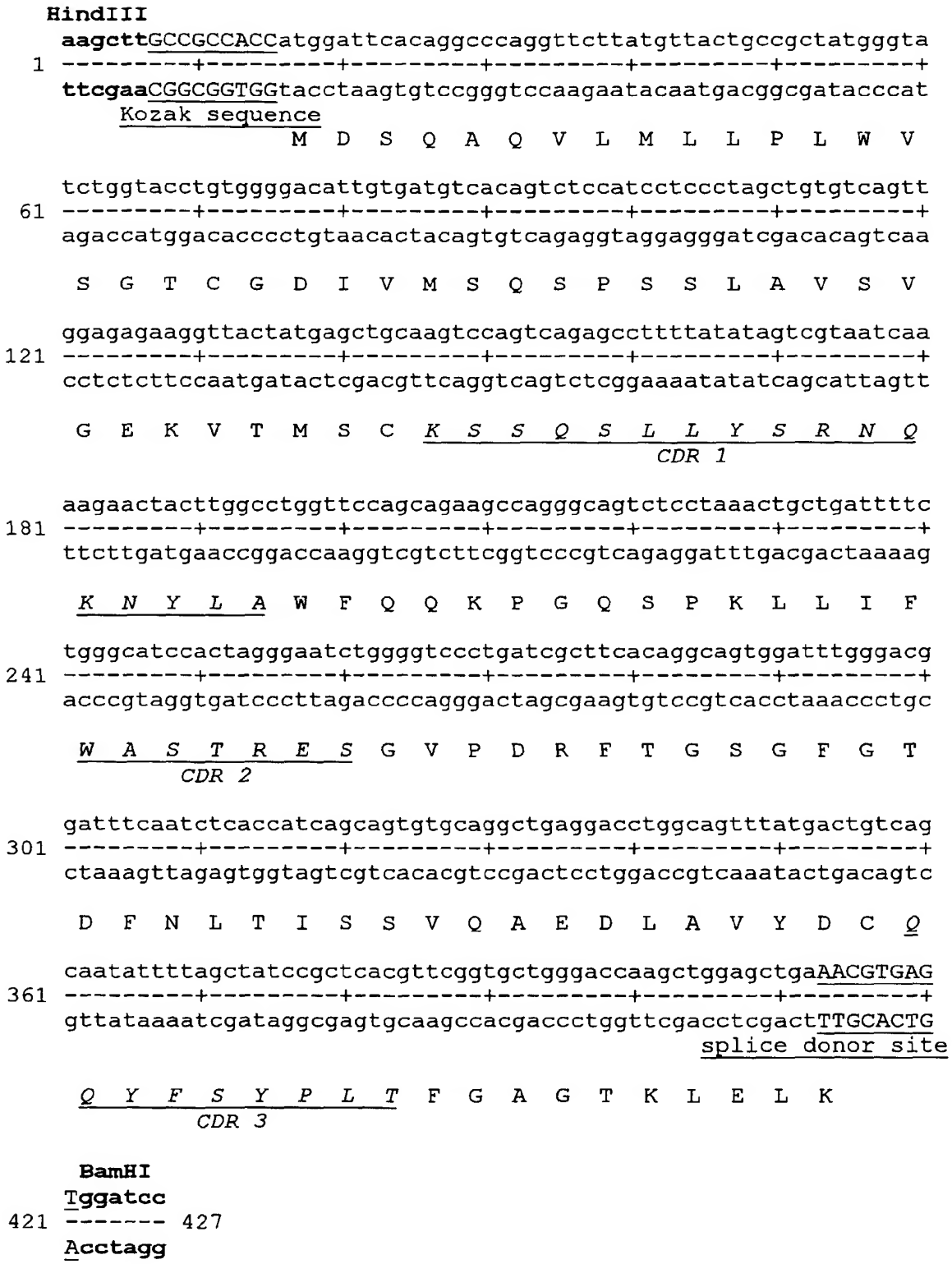
HindIII
aagcttGCCGCCACCatggattcacaggcccaggttcttatgttactgccgctatgggta
ttcgaaCGGCGGTGGtacctaagtgtccgggtccaagaatacaatgacggcgatacccat
Kozak sequence
M D S Q A Q V L M L L P L W V
tctggtacctgtggggacattgtgatgtcacagtctccatcctccctagctgtgtcagtt
agaccatggacacccctgtaacactacagtgtcagaggtaggagggatcgacacagtcaa
S G T C G D I V M S Q S P S S L A V S V
ggagagaaggttactatgagctgcaagtccagtcagagccttttatatagtcgtaatcaa
cctctcttccaatgatactcgacgttcaggtcagtctcggaaaatatatcagcattagtt
G E K V T M S C K S S Q S L L Y S R N Q
CDR 1
aagaactacttggcctggttccagcagaagccagggcagtctcctaaactgctgatttc
ttcttgatgaaccggaccaaggtcgtcttcggtcccgtcagaggatttgacgactaaaag
K N Y L A W F Q Q K P G Q S P K L L I F
tgggcatccactagggaatctggggtccctgatcgcttcacaggcagtggatttgggacg
acccgtaggtgatcccttagaccccagggactagcgaagtgtccgtcacctaaaccctgc
W A S T R E S G V P D R F T G S G F G T
CDR 2
gatttcaatctcaccatcagcagtgtgcaggctgaggacctggcagtttatgactgtcag
ctaaagttagagtggtagtcgtcacacgtccgactcctggaccgtcaaatactgacagtc
D F N L T I S S V Q A E D L A V Y D C Q
caatattttagctatccgctcacgttcggtgctgggaccaagctggagctgaAACGTGAG
gttataaaatcgataggcgagtgcaagccacgaccctggttcgacctcgactTTGCACTG
splice donor site
Q Y F S Y P L T F G A G T K L E L K
CDR 3
BamHI
Tggatcc
------- 427
Acctagg

Fig. 25

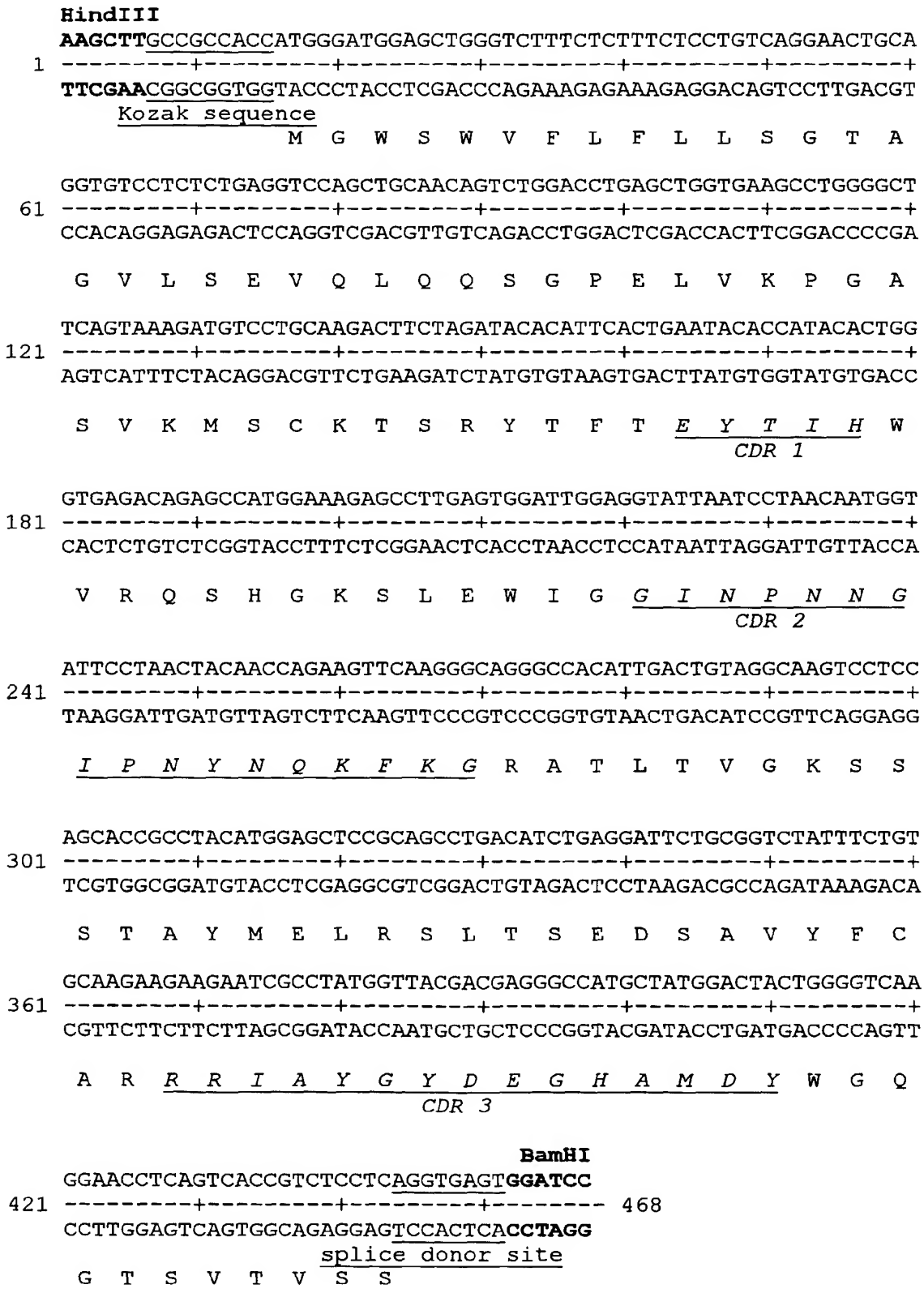
HindIII
AAGCTTGCCGCCACCATGGGATGGAGCTGGGTCTTTCTCTTTCTCCTGTCAGGAACTGCA
TTCGAACGGCGGTGGTACCCTACCTCGACCCAGAAAGAGAAAGAGGACAGTCCTTGACGT
Kozak sequence
M G W S W V F L F L L S G T A
GGTGTCCTCTCTGAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCT
CCACAGGAGAGACTCCAGGTCGACGTTGTCAGACCTGGACTCGACCACTTCGGACCCCGA
G V L S E V Q L Q Q S G P E L V K P G A
TCAGTAAAGATGTCCTGCAAGACTTCTAGATACACATTCACTGAATACACCATACACTGG
AGTCATTTCTACAGGACGTTCTGAAGATCTATGTGTAAGTGACTTATGTGGTATGTGACC
S V K M S C K T S R Y T F T E Y T I H W
CDR 1
GTGAGACAGAGCCATGGAAAGAGCCTTGAGTGGATTGGAGGTATTAATCCTAACAATGGT
CACTCTGTCTCGGTACCTTTCTCGGAACTCACCTAACCTCCATAATTAGGATTGTTACCA
V R Q S H G K S L E W I G G I N P N N G
CDR 2
ATTCCTAACTACAACCAGAAGTTCAAGGGCAGGGCCACATTGACTGTAGGCAAGTCCTCC
TAAGGATTGATGTTAGTCTTCAAGTTCCCGTCCCGGTGTAACTGACATCCGTTCAGGAGG
I P N Y N Q K F K G R A T L T V G K S S
AGCACCGCCTACATGGAGCTCCGCAGCCTGACATCTGAGGATTCTGCGGTCTATTTCTGT
TCGTGGCGGATGTACCTCGAGGCGTCGGACTGTAGACTCCTAAGACGCCAGATAAAGACA
S T A Y M E L R S L T S E D S A V Y F C
GCAAGAAGAAGAATCGCCTATGGTTACGACGAGGGCCATGCTATGGACTACTGGGGTCAA
CGTTCTTCTTCTTAGCGGATACCAATGCTGCTCCCGGTACGATACCTGATGACCCCAGTT
A R R R I A Y G Y D E G H A M D Y W G Q
CDR 3
BamHI
GGAACCTCAGTCACCGTCTCCTCAGGTGAGTGGATCC
CCTTGGAGTCAGTGGCAGAGGAGTCCACTCACCTAGG
splice donor site
G T S V T V S S

Fig. 26 /1

```
                                        Spe I
   1  gaattccagc acactggcgg ccgttACTAG TTATTAATAG TAATCAATTA

  51  CGGGGTCATT AGTTCATAGC CCATATATGG AGTTCCGCGT TACATAACTT

 101  ACGGTAAATG GCCCGCCTGG CTGACCGCCC AACGACCCCC GCCCATTGAC

 151  GTCAATAATG ACGTATGTTC CCATAGTAAC GCCAATAGGG ACTTTCCATT

 201  GACGTCAATG GGTGGAGTAT TTACGGTAAA CTGCCCACTT GGCAGTACAT

 251  CAAGTGTATC ATATGCCAAG TACGCCCCCT ATTGACGTCA ATGACGGTAA

 301  ATGGCCCGCC TGGCATTATG CCCAGTACAT GACCTTATGG GACTTTCCTA
                    SnaB I
 351  CTTGGCAGTA CATCTACGTA TTAGTCATCG CTATTACCAT GGTGATGCGG

 401  TTTTGGCAGT ACATCAATGG GCGTGGATAG CGGTTTGACT CACGGGGATT

 451  TCCAAGTCTC CACCCCATTG ACGTCAATGG GAGTTTGTTT TGGCACCAAA

 501  ATCAACGGGA CTTTCCAAAA TGTCGTAACA ACTCCGCCCC ATTGACGCAA

 551  ATGGGCGGTA GGCGTGTACG GTGGGAGGTC TATATAAGCA GAGCTCGTTT

 601  AGTGAACCGT CAGATCGCCT GGAGACGCCA TCCACGCTGT TTTGACCTCC
                                        Sac II
 651  ATAGAAGACA CCGGGACCGA TCCAGCCTCC GCGGCCGGGA ACGGTGCATT

 701  GGAACGCGGA TTCCCCGTGC CAAGAGTGAC GTAAGTACCG CCTATAGAGT

 751  CTATAGGCCC ACCCCCTTGG CTTCTTATGC ATGCTATACT GTTTTTGGCT

 801  TGGGGTCTAT ACACCCCCGC TTCCTCATGT TATAGGTGAT GGTATAGCTT

 851  AGCCTATAGG TGTGGGTTAT TGACCATTAT TGACCACTCC CCTATTGGTG

 901  ACGATACTTT CCATTACTAA TCCATAACAT GGCTCTTTGC CACAACTCTC

 951  TTTATTGGCT ATATGCCAAT ACACTGTCCT TCAGAGACTG ACACGGACTC

1001  TGTATTTTTA CAGGATGGGG TCTCATTTAT TATTTACAAA TTCACATATA

1051  CAACACCACC GTCCCCAGTG CCCGCAGTTT TTATTAAACA TAACGTGGGA
                                        BspE I
1101  TCTCCACGCG AATCTCGGGT ACGTGTTCCG GACATGGGCT CTTCTCCGGT

1151  AGCGGCGGAG CTTCTACATC CGAGCCCTGC TCCCATGCCT CCAGCGACTC

1201  ATGGTCGCTC GGCAGCTCCT TGCTCCTAAC AGTGGAGGCC AGACTTAGGC

1251  ACAGCACGAT GCCCACCACC ACCAGTGTGC CGCACAAGGC CGTGGCGGTA
```

Fig. 26 /2

```
1301  GGGTATGTGT CTGAAAATGA GCTCggggag cgggcttgca ccgctgacgc
                  Afl II
1351  atttggaaga cttaaggcag cggcagaaga agatgcaggc agctgagttg

1401  ttgtgttctg ataagagtca gaggtaactc ccgttgcggt gctgttaacg

1451  gtggagggca gtgtagtctg agcagtactc gttgctgccg cgcgccgcac

1501  cagacataat agctgacaga ctaacagact gttcctttcc atgggtcttt
                              Mlu I        Hind III
1551  tctgcagtca ccgtccttga cacgcgtctc gggaagcttG CCGCCACCAT
                                                        M
                                                     Kpn I
1601  GGATTCACAG GCCCAGGTTC TTATGTTACT GCCGCTATGG GTATCTGGTA
        D  S  Q   A  Q  V   L  M  L  L   P  L  W   V  S  G

1651  CCTGTGGGGA CATTGTGATG TCACAGTCTC CATCCTCCCT AGCTGTGTCA
      T  C  G  D   I  V  M   S  Q  S   P  S  S  L   A  V  S

1701  GTTGGAGAGA AGGTTACTAT GAGCTGCAAG TCCAGTCAGA GCCTTTTATA
       V  G  E   K  V  T  M   S  C  K  S  S  Q  S  L  L  Y
        XbaI                                  CDR 1
1751  TTCTAGAAAT CAAAAGAACT ACTTGGCCTG GTTCCAGCAG AAGCCAGGGC
        S  R  N   Q  K  N   Y  L  A  W   F  Q  Q   K  P  G

1801  AGTCTCCTAA ACTGCTGATT TTCTGGGCAT CCACTAGGGA ATCTGGGGTC
      Q  S  P  K   L  L  I   F  W  A  S  T  R  E  S  G  V
                                      CDR 2
1851  CCTGATCGCT TCACAGGCAG TGGATTTGGG ACGGATTTCA ATCTCACCAT
       P  D  R   F  T  G  S   G  F  G   T  D  F   N  L  T  I

1901  CAGCAGTGTG CAGGCTGAGG ACCTGGCAGT TTATGACTGT CAGCAATATT
        S  S  V   Q  A  E   D  L  A  V   Y  D  C   Q  Q  Y

1951  TTAGCTATCC GCTCACGTTC GGTGCTGGGA CCAAGCTGGA GCTGAAACGT
      F  S  Y  P   L  T  F   G  A  G   T  K  L  E   L  K  R
            CDR 3
        BamH I
2001  GAGTggatcc ATCTGGGATA AGCATGCTGT TTTCTGTCTG TCCCTAACAT

2051  GCCCTGTGAT TATGCGCAAA CAACACACCC AAGGGCAGAA CTTTGTTACT

2101  TAAACACCAT CCTGTTTGCT TCTTTCCTCA GGAACTGTGG CTGCACCATC
                                        T  V   A  A  P  S
2151  TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT GGAACTGCCT
       V  F  I   F  P  P   S  D  E  Q   L  K  S   G  T  A
2201  CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC CAAAGTACAG
      S  V  V  C   L  L  N   N  F  Y   P  R  E  A   K  V  Q
2251  TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG AGAGTGTCAC
       W  K  V   D  N  A  L   Q  S  G   N  S  Q   E  S  V  T
2301  AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC ACCCTGACGC
       E  Q  D   S  K  D   S  T  Y  S   L  S  S   T  L  T
```

Fig. 26 /3

```
2351  TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC
        L  S  K  A   D  Y  E   K  H  K   V  Y  A  C   E  V  T
2401  CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG
        H  Q  G   L  S  S  P   V  T  K   S  F  N  R   G  E  C
2451  TTAGAGGGAG AAGTGCCCCC ACCTGCTCCT CAGTTCCAGC CTGACCCCCT
        *
2501  CCCATCCTTT GGCCTCTGAC CCTTTTTCCA CAGGGGACCT ACCCCTATTG

2551  CGGTCCTCCA GCTCATCTTT CACCTCACCC CCCTCCTCCT CCTTGGCTTT

2601  AATTATGCTA ATGTTGGAGG AGAATGAATA AATAAAGTGA ATCTTTGCAC

2651  CTGTGGTGGA TCTAATAAAA GATATTTATT TTCATTAGAT ATGTGTGTTG

2701  GTTTTTTGTG TGCAGTGCCT CTATCTGGAG GCCAGGTAGG GCTGGCCTTG

2751  GGGGAGGGGG AGGCCAGAAT GACTCCAAGA GCTACAGGAA GGCAGGTCAG

2801  AGACCCCACT GGACAAACAG TGGCTGGACT CTGCACCATA ACACACAATC

2851  AACAGGGGAG TGAGCTGGAA ATTTGCTAGC GAATTCTTGA AGACGAAAGG

2901  GCCTCGTGAT ACGCCTATTT TTATAGGTTA ATGTCATGAT AATAATGGTT

2951  TCTTAGACGT CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT

3001  TTGTTTATTT TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT

3051  AACCCTGATA AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT

3101  CAACATTTCC GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC

3151  TGTTTTTGCT CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAAGATC

3201  AGTTGGGTGC ACGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG

3251  ATCCTTGAGA GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT

3301  TAAAGTTCTG CTATGTGGCG CGGTATTATC CCGTGTTGAC GCCGGGCAAG

3351  AGCAACTCGG TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC

3401  TCACCAGTCA CAGAAAAGCA TCTTACGGAT GGCATGACAG TAAGAGAATT

3451  ATGCAGTGCT GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC
            Pvu I
3501  TGACAACGAT CGGAGGACCG AAGGAGCTAA CCGCTTTTTT GCACAACATG

3551  GGGGATCATG TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC

3601  CATACCAAAC GACGAGCGTG ACACCACGAT GCCTGCAGCA ATGGCAACAA
```

Fig. 26 /4

```
3651  CGTTGCGCAA ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA
3701  CAATTAATAG ACTGGATGGA GGCGGATAAA GTTGCAGGAC CACTTCTGCG
3751  CTCGGCCCTT CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG
3801  AGCGTGGGTC TCGCGGTATC ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC
3851  TCCCGTATCG TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA
3901  ACGAAATAGA CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTGGT
3951  AACTGTCAGA CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT
4001  CATTTTTAAT TTAAAAGGAT CTAGGTGAAG ATCCTTTTTG ATAATCTCAT
4051  GACCAAAATC CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG
4101  TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT GCGCGTAATC
4151  TGCTGCTTGC AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC
4201  GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG
4251  CGCAGATACC AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC
4301  TTCAAGAACT CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT
4351  ACCAGTGGCT GCTGCCAGTG GCGATAAGTC GTGTCTTACC GGGTTGGACT
4401  CAAGACGATA GTTACCGGAT AAGGCGCAGC GGTCGGGCTG AACGGGGGGT
4451  TCGTGCACAC AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA
4501  CCTACAGCGT GAGCTATGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG
4551  CGGACAGGTA TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG
4601  GAGCTTCCAG GGGGAAACGC CTGGTATCTT TATAGTCCTG TCGGGTTTCG
4651  CCACCTCTGA CTTGAGCGTC GATTTTTGTG ATGCTCGTCA GGGGGGCGGA
4701  GCCTATGGAA AAACGCCAGC AACGCGGCCT TTTTACGGTT CCTGGCCTTT
                          BspLU11I
4751  TGCTGGCCTT TTGCTCACAT GTTCTTTCCT GCGTTATCCC CTGATTCTGT
4801  GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT CGCCGCAGCC
4851  GAACGACCGA GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCCTG
4901  ATGCGGTATT TTCTCCTTAC GCATCTGTGC GGTATTTCAC ACCGCATATG
```

Fig. 26 /5

```
                                                          Bst1107I
4951  GTGCACTCTC AGTACAATCT GCTCTGATGC CGCATAGTTA AGCCAGTATA
5001  CACTCCGCTA TCGCTACGTG ACTGGGTCAT GGCTGCGCCC CGACACCCGC
5051  CAACACCCGC TGACGCGCCC TGACGGGCTT GTCTGCTCCC GGCATCCGCT
5101  TACAGACAAG CTGTGACCGT CTCCGGGAGC TGCATGTGTC AGAGGTTTTC
5151  ACCGTCATCA CCGAAACGCG CGAGGCAGCT GTGGAATGTG TGTCAGTTAG
5201  GGTGTGGAAA GTCCCCAGGC TCCCCAGCAG GCAGAAGTAT GCAAAGCATG
5251  CATCTCAATT AGTCAGCAAC CAGGCTCCCC AGCAGGCAGA AGTATGCAAA
5301  GCATGCATCT CAATTAGTCA GCAACCATAG TCCCGCCCCT AACTCCGCCC
5351  ATCCCGCCCC TAACTCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG
                                                  Sfi I
5401  ACTAATTTTT TTTATTTATG CAGAGGCCGA GGCCGCCTCG GCCTCTGAGC
                                               Stu I/Avr II
5451  TATTCCAGAA GTAGTGAGGA GGCTTTTTTG GAGGCCTAGG CTTTTGCAAA
5501  AAGCTAGCTT CACGCTGCCG CAAGCACTCA GGGCGCAAGG GCTGCTAAAG
5551  GAAGCGGAAC ACGTAGAAAG CCAGTCCGCA GAAACGGTGC TGACCCCGGA
5601  TGAATGTCAG CTACTGGGCT ATCTGGACAA GGGAAAACGC AAGCGCAAAG
5651  AGAAAGCAGG TAGCTTGCAG TGGGCTTACA TGGCGATAGC TAGACTGGGC
5701  GGTTTTATGG ACAGCAAGCG AACCGGAATT GCCAGCTGGG GCGCCCTCTG
5751  GTAAGGTTGG GAAGCCCTGC AAAGTAAACT GGATGGCTTT CTTGCCGCCA
                                  Bgl II/Bcl I
5801  AGGATCTGAT GGCGCAGGGG ATCAAGATCT GATCAAGAGA CAGGATGAGG
5851  ATCGTTTCGC ATGATTGAAC AAGATGGATT GCACGCAGGT TCTCCGGCCG
5901  CTTGGGTGGA GAGGCTATTC GGCTATGACT GGGCACAACA GACAATCGGC
5951  TGCTCTGATG CCGCCGTGTT CCGGCTGTCA GCGCAGGGGC GCCCGGTTCT
6001  TTTTGTCAAG ACCGACCTGT CCGGTGCCCT GAATGAACTG CAGGACGAGG
                              Msc I
6051  CAGCGCGGCT ATCGTGGCTG GCCACGACGG GCGTTCCTTG CGCAGCTGTG
6101  CTCGACGTTG TCACTGAAGC GGGAAGGGAC TGGCTGCTAT TGGGCGAAGT
6151  GCCGGGGCAG GATCTCCTGT CATCTCACCT TGCTCCTGCC GAGAAAGTAT
6201  CCATCATGGC TGATGCAATG CGGCGGCTGC ATACGCTTGA TCCGGCTACC
```

Fig. 26 /6

```
6251  TGCCCATTCG ACCACCAAGC GAAACATCGC ATCGAGCGAG CACGTACTCG

6301  GATGGAAGCC GGTCTTGTCG ATCAGGATGA TCTGGACGAA GAGCATCAGG

6351  GGCTCGCGCC AGCCGAACTG TTCGCCAGGC TCAAGGCGCG CATGCCCGAC

6401  GGCGAGGATC TCGTCGTGAC CCATGGCGAT GCCTGCTTGC CGAATATCAT

6451  GGTGGAAAAT GGCCGCTTTT CTGGATTCAT CGACTGTGGC CGGCTGGGTG
          Rsr II
6501  TGGCGGACCG CTATCAGGAC ATAGCGTTGG CTACCCGTGA TATTGCTGAA

6551  GAGCTTGGCG GCGAATGGGC TGACCGCTTC CTCGTGCTTT ACGGTATCGC

6601  CGCTCCCGAT TCGCAGCGCA TCGCCTTCTA TCGCCTTCTT GACGAGTTCT
                                 Nsp V
6651  TCTGAGCGGG ACTCTGGGGT TCGAAATGAC CGACCAAGCG ACGCCCAACC

6701  TGCCATCACG AGATTTCGAT TCCACCGCCG CCTTCTATGA AAGGTTGGGC

6751  TTCGGAATCG TTTTCCGGGA CGCCGGCTGG ATGATCCTCC AGCGCGGGGA
                                       Sma I                Nru I
6801  TCTCATGCTG GAGTTCTTCG CCCACCCCGG GCTCGATCCC CTCGCGAGTT

6851  GGTTCAGCTG CTGCCTGAGG CTGGACGACC TCGCGGAGTT CTACCGGCAG

6901  TGCAAATCCG TCGGCATCCA GGAAACCAGC AGCGGCTATC CGCGCATCCA

6951  TGCCCCCGAA CTGCAGGAGT GGGGAGGCAC GATGGCCGCT TTGGTCCCGG

7001  ATCTTTGTGA AGGAACCTTA CTTCTGTGGT GTGACATAAT TGGACAAACT

7051  ACCTACAGAG ATTTAAAGCT CTAAGGTAAA TATAAAATTT TTAAGTGTAT

7101  AATGTGTTAA ACTACTGATT CTAATTGTTT GTGTATTTTA GATTCCAACC

7151  TATGGAACTG ATGAATGGGA GCAGTGGTGG AATGCCTTTA ATGAGGAAAA

7201  CCTGTTTTGC TCAGAAGAAA TGCCATCTAG TGATGATGAG GCTACTGCTG

7251  ACTCTCAACA TTCTACTCCT CCAAAAAAGA AGAGAAAGGT AGAAGACCCC

7301  AAGGACTTTC CTTCAGAATT GCTAAGTTTT TTGAGTCATG CTGTGTTTAG

7351  TAATAGAACT CTTGCTTGCT TTGCTATTTA CACCACAAAG GAAAAAGCTG

7401  CACTGCTATA CAAGAAAATT ATGGAAAAAT ATTCTGTAAC CTTTATAAGT

7451  AGGCATAACA GTTATAATCA TAACATACTG TTTTTTCTTA CTCCACACAG

7501  GCATAGAGTG TCTGCTATTA ATAACTATGC TCAAAAATTG TGTACCTTTA
```

Fig. 26 /7

```
7551  GCTTTTTAAT TTGTAAAGGG GTTAATAAGG AATATTTGAT GTATAGTGCC

7601  TTGACTAGAG ATCATAATCA GCCATACCAC ATTTGTAGAG GTTTTACTTG

7651  CTTTAAAAAA CCTCCCACAC CTCCCCCTGA ACCTGAAACA TAAAATGAAT
        Mun I
7701  GCAATTGTTG TTGTTAACTT GTTTATTGCA GCTTATAATG GTTACAAATA

7751  AAGCAATAGC ATCACAAATT TCACAAATAA AGCATTTTTT TCACTGCATT

7801  CTAGTTGTGG TTTGTCCAAA CTCATCAATG TATCTTATCA TGTCTGGATC

7851  TAATAAAAGA TATTTATTTT CATTAGATAT GTGTGTTGGT TTTTTGTGTG

7901  CAGTGCCTCT ATCTGGAGGC CAGGTAGGGC TGGCCTTGGG GGAGGGGGAG

7951  GCCAGAATGA CTCCAAGAGC TACAGGAAGG CAGGTCAGAG ACCCCACTGG

8001  ACAAACAGTG GCTGGACTCT GCACCATAAC ACACAATCAA CAGGGGAGTG

8051  AGCTGGAAAT TTGCTAGC
```

Fig. 27/1

```
   1 TTGAAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAAT

  61 GGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTT

 121 ATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCT

 181 TCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCC

 241 CTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAA

 301 AGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGG

 361 TAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGT

 421 TCTGCTATGTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCG

 481 CATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTAC

 541 GGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGC
                            Pvu I
 601 GGCCAACTTACTTCTGACAACGATCGGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAA

 661 CATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACC
                                                          Fsp I
 721 AAACGACGAGCGTGACACCACGATGCCTGCAGCAATGGCAACAACGTTGCGCAAACTATT

 781 AACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGA
```

Fig. 27 /2

```
 841 TAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAA

 901 ATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAA

 961 GCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAA

1021 TAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGT

1081 TTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGT

1141 GAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTG

1201 AGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGT

1261 AATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCA

1321 AGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATAC

1381 TGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTAC

1441 ATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCT

1501 TACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGG

1561 GGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACA

1621 GCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGT

1681 AAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTA

1741 TCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTC

1801 GTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGC
                          BspLU11I
1861 CTTTTGCTGGCCTTTTGCTC**ACATGT**TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAA

1921 CCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAG

1981 CGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCTGATGCGGTATTTTCTCCTTACGCATCT

2041 GTGCGGTATTTCACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATA
            Bst1107 I
2101 GTTAAGCCA**GTATAC**ACTCCGCTATCGCTACGTGACTGGGTCATGGCTGCGCCCCGACAC

2161 CCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGA

2221 CAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAA

2281 CGCGCGAGGCAGCATGCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCC

2341 CATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTT
                                  Sfi I
2401 TTTTATTTATGCAGAGGCCGA**GGCC**GCCTC**GGCC**TCTGAGCTATTCCAGAAGTAGTGAGG
                 Stu I/Avr II
2461 AGGCTTTTTTGG**AGGCCTAGG**CTTTTGCAAAAAGCTAGCTTACAGCTCAGGGCTGCGATT
```

Fig. 27 /3

```
2521 TCGCGCCAAACTTGACGGCAATCCTAGCGTGAAGGCTGGTAGGATTTTATCCCCGCTGCC

2581 ATCATGGTTCGACCATTGAACTGCATCGTCGCCGTGTCCCAAAATATGGGGATTGGCAAG

2641 AACGGAGACCTACCCTGGCCTCCGCTCAGGAACGAGTTCAAGTACTTCCAAAGAATGACC

2701 ACAACCTCTTCAGTGGAAGGTAAACAGAATCTGGTGATTATGGGTAGGAAAACCTGGTTC

2761 TCCATTCCTGAGAAGAATCGACCTTTAAAGGACAGAATTAATATAGTTCTCAGTAGAGAA

2821 CTCAAAGAACCACCACGAGGAGCTCATTTTCTTGCCAAAAGTTTGGATGATGCCTTAAGA

2881 CTTATTGAACAACCGGAATTGGCAAGTAAAGTAGACATGGTTTGGATAGTCGGAGGCAGT

2941 TCTGTTTACCAGGAAGCCATGAATCAACCAGGCCACCTCAGACTCTTTGTGACAAGGATC

3001 ATGCAGGAATTTGAAAGTGACACGTTTTTCCCAGAAATTGATTTGGGGAAATATAAACTT

3061 CTCCCAGAATACCCAGGCGTCCTCTCTGAGGTCCAGGAGGAAAAAGGCATCAAGTATAAG

3121 TTTGAAGTCTACGAGAAGAAAGACTAACAGGAAGATGCTTTCAAGTTCTCTGCTCCCCTC
                                                    Bgl II
3181 CTAAAGCTATGCATTTTTATAAGACCATGGGACTTTTGCTGGCTTTAGATCTTTGTGAAG

3241 GAACCTTACTTCTGTGGTGTGACATAATTGGACAAACTACCTACAGAGATTTAAAGCTCT

3301 AAGGTAAATATAAAATTTTTAAGTGTATAATGTGTTAAACTACTGATTCTAATTGTTTGT

3361 GTATTTTAGATTCCAACCTATGGAACTGATGAATGGGAGCAGTGGTGGAATGCCTTTAAT

3421 GAGGAAAACCTGTTTTGCTCAGAAGAAATGCCATCTAGTGATGATGAGGCTACTGCTGAC

3481 TCTCAACATTCTACTCCTCCAAAAAAGAAGAGAAAGGTAGAAGACCCCAAGGACTTTCCT

3541 TCAGAATTGCTAAGTTTTTTGAGTCATGCTGTGTTTAGTAATAGAACTCTTGCTTGCTTT

3601 GCTATTTACACCACAAAGGAAAAAGCTGCACTGCTATACAAGAAAATTATGGAAAAATAT

3661 TCTGTAACCTTTATAAGTAGGCATAACAGTTATAATCATAACATACTGTTTTTTCTTACT

3721 CCACACAGGCATAGAGTGTCTGCTATTAATAACTATGCTCAAAAATTGTGTACCTTTAGC

3781 TTTTTAATTTGTAAAGGGGTTAATAAGGAATATTTGATGTATAGTGCCTTGACTAGAGAT
    BsaB I
3841 CATAATCAGCCATACCACATTTGTAGAGGTTTTACTTGCTTTAAAAAACCTCCCACACCT
                                        Mun I
3901 CCCCCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTGTTAACTTGTTTATTGCAGC

3961 TTATAATGGTTACAAATAAAGCAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTC

4021 ACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGGATCTA

4081 ATAAAAGATATTTATTTTCATTAGATATGTGTGTTGGTTTTTTGTGTGCAGTGCCTCTAT

4141 CTGGAGGCCAGGTAGGGCTGGCCTTGGGGGAGGGGGAGGCCAGAATGACTCCAAGAGCTA

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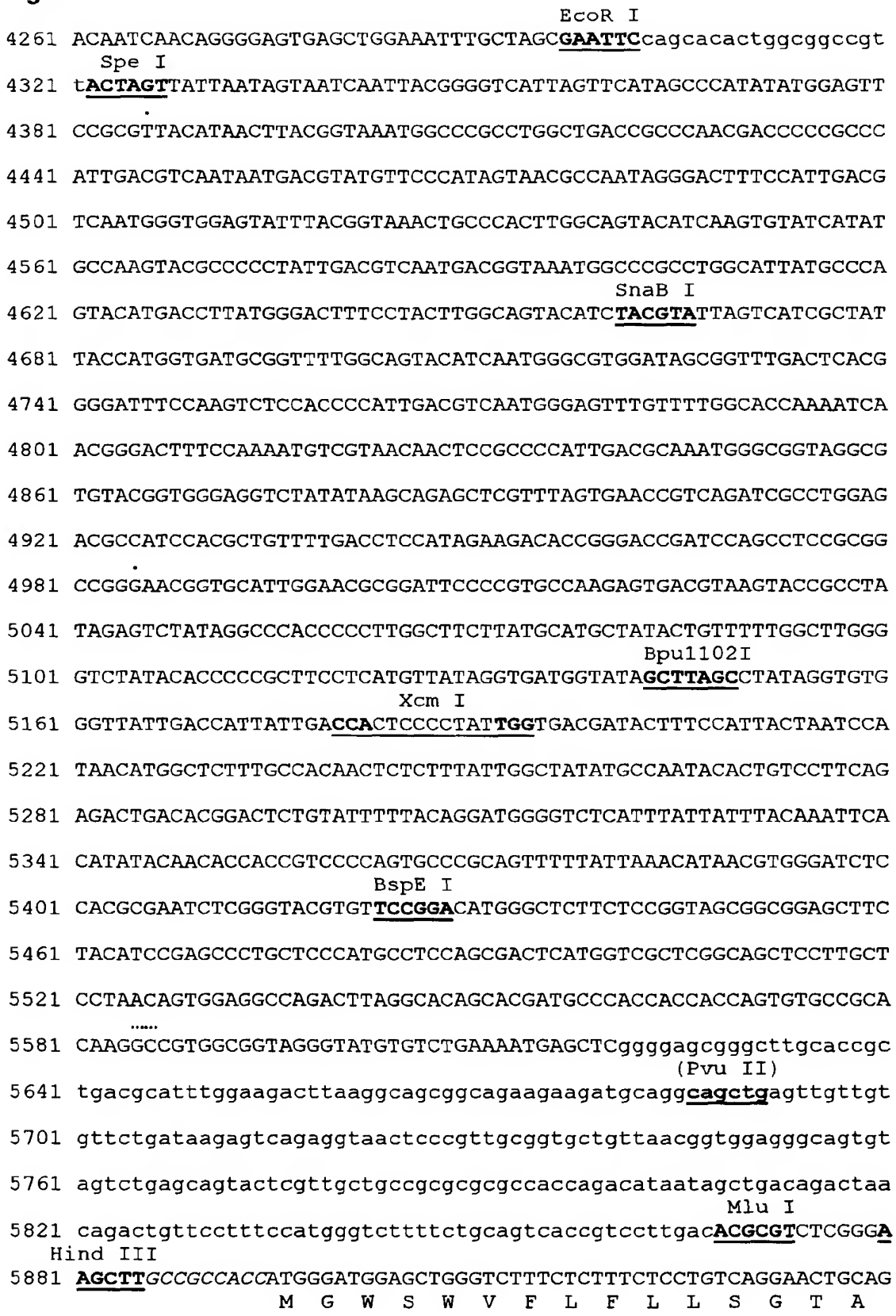
Fig. 27 /4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SnaB I
4621 GTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTAT
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4921 ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGG
4981 CCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTA
5041 TAGAGTCTATAGGCCCACCCCCTTGGCTTCTTATGCATGCTATACTGTTTTTGGCTTGGG
Bpu1102I
5101 GTCTATACACCCCCGCTTCCTCATGTTATAGGTGATGGTATAGCTTAGCCTATAGGTGTG
Xcm I
5161 GGTTATTGACCATTATTGACCCACTCCCCTATTGGTGACGATACTTTCCATTACTAATCCA
5221 TAACATGGCTCTTTGCCACAACTCTCTTTATTGGCTATATGCCAATACACTGTCCTTCAG
5281 AGACTGACACGGACTCTGTATTTTTACAGGATGGGGTCTCATTTATTATTTACAAATTCA
5341 CATATACAACACCACCGTCCCCAGTGCCCGCAGTTTTTATTAAACATAACGTGGGATCTC
BspE I
5401 CACGCGAATCTCGGGTACGTGTTCCGGACATGGGCTCTTCTCCGGTAGCGGCGGAGCTTC
5461 TACATCCGAGCCCTGCTCCCATGCCTCCAGCGACTCATGGTCGCTCGGCAGCTCCTTGCT
5521 CCTAACAGTGGAGGCCAGACTTAGGCACAGCACGATGCCCACCACCACCAGTGTGCCGCA
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5761 agtctgagcagtactcgttgctgccgcgcgccaccagacataatagctgacagactaa
Mlu I
5821 cagactgttcctttccatgggtcttttctgcagtcaccgtccttgacACGCGTCTCGGGA
Hind III
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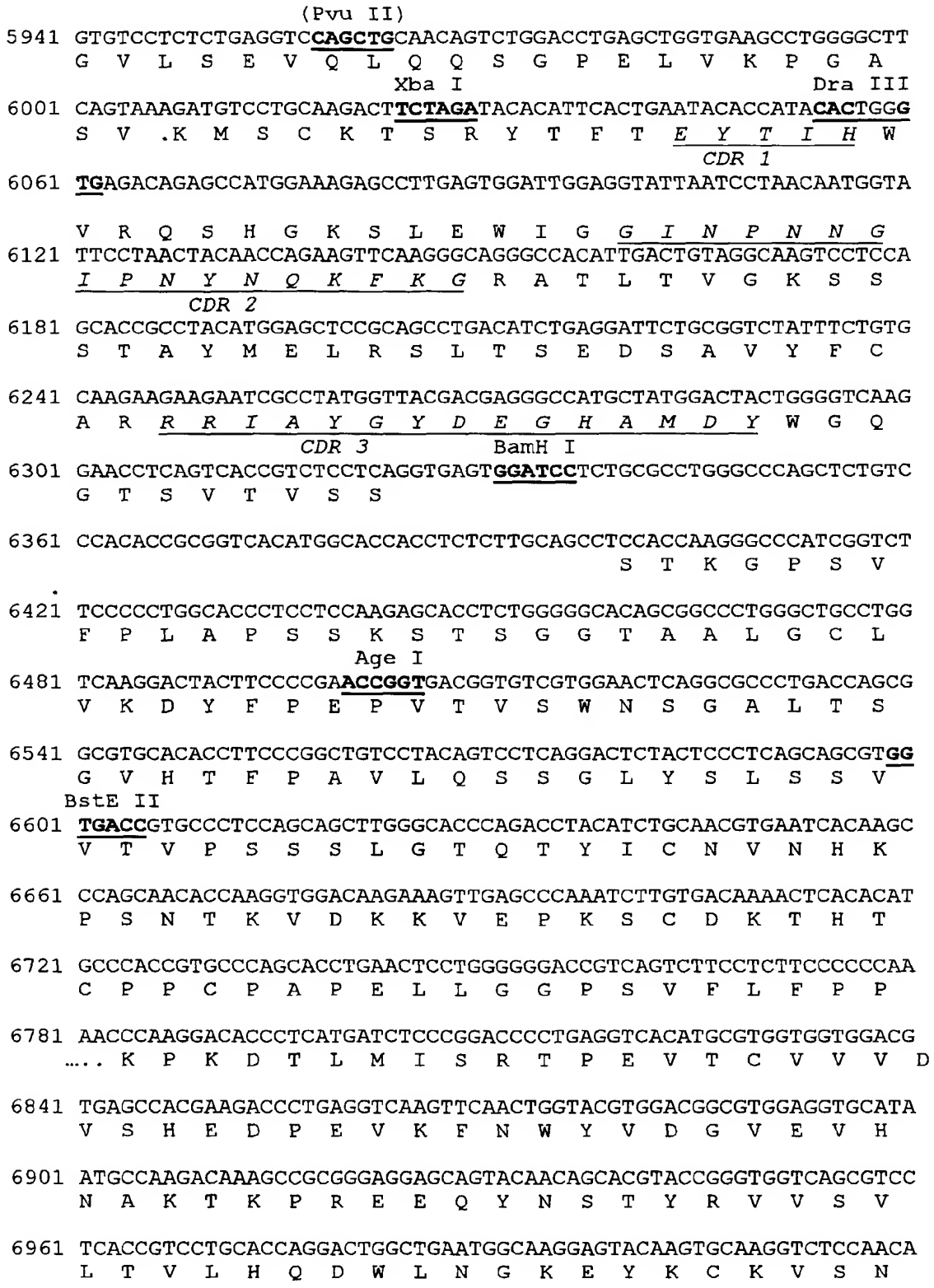
Fig. 27 /5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Dra III
6001 CAGTAAAGATGTCCTGCAAGACTTCTAGATACACATTCACTGAATACACCATACACTGGG
S V .K M S C K T S R Y T F T E Y T I H W
CDR 1
6061 TGAGACAGAGCCATGGAAAGAGCCTTGAGTGGATTGGAGGTATTAATCCTAACAATGGTA
V R Q S H G K S L E W I G G I N P N N G
6121 TTCCTAACTACAACCAGAAGTTCAAGGGCAGGGCCACATTGACTGTAGGCAAGTCCTCCA
I P N Y N Q K F K G R A T L T V G K S S
CDR 2
6181 GCACCGCCTACATGGAGCTCCGCAGCCTGACATCTGAGGATTCTGCGGTCTATTTCTGTG
S T A Y M E L R S L T S E D S A V Y F C
6241 CAAGAAGAAGAATCGCCTATGGTTACGACGAGGGCCATGCTATGGACTACTGGGGTCAAG
A R R R I A Y G Y D E G H A M D Y W G Q
CDR 3
BamH I
6301 GAACCTCAGTCACCGTCTCCTCAGGTGAGTGGATCCTCTGCGCCTGGGCCCAGCTCTGTC
G T S V T V S S
6361 CCACACCGCGGTCACATGGCACCACCTCTCTTGCAGCCTCCACCAAGGGCCCATCGGTCT
S T K G P S V
6421 TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGG
F P L A P S S K S T S G G T A A L G C L
Age I
6481 TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCG
V K D Y F P E P V T V S W N S G A L T S
6541 GCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG
G V H T F P A V L Q S S G L Y S L S S V
BstE II
6601 TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGC
V T V P S S S L G T Q T Y I C N V N H K
6661 CCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACAT
P S N T K V D K K V E P K S C D K T H T
6721 GCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA
C P P C P A P E L L G G P S V F L F P P
6781 AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACG
..... K P K D T L M I S R T P E V T C V V V D
6841 TGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA
V S H E D P E V K F N W Y V D G V E V H
6901 ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCC
N A K T K P R E E Q Y N S T Y R V V S V
6961 TCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
L T V L H Q D W L N G K E Y K C K V S N

Fig. 27 /6

```
7021 AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
     K  A  L  P  A  P  I  E  K  T  I  S  K  A  K  G  Q  P  R  E

7081 CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGA
     P  Q  V  Y  T  L  P  P  S  R  E  E  M  T  K  N  Q  V  S  L

7141 CCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
     T  C  L  V  K  G  F  Y  P  S  D  I  A  V  E  W  E  S  N  G

7201 AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
     Q  P  E  N  N  Y  K  T  T  P  P  V  L  D  S  D  G  S  F  F

7261 TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
     L  Y  S  K  L  T  V  D  K  S  R  W  Q  Q  G  N  V  F  S  C

7321 CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
     S  V  M  H  E  A  L  H  N  H  Y  T  Q  K  S  L  S  L  S  P
                       NgoM I
7381 GTAAATGAGTGCGACGGCCGGCAAGCCCCGCTCCCCGGGCTCTCGCGGTCGCACGAGGAT
     G  K  *
7441 GCTTGGCACGTACCCCCTGTACATACTTCCCGGGCGCCCAGCATGGAAATAAAGCACCGG

7501 ATCTAATAAAAGATATTTATTTTCATTAGATATGTGTGTTGGTTTTTTGTGTGCAGTGCC

7561 TCTATCTGGAGGCCAGGTAGGGCTGGCCTTGGGGGAGGGGGAGGCCAGAATGACTCCAAG

7621 AGCTACAGGAAGGCAGGTCAGAGACCCCACTGGACAAACAGTGGCTGGACTCTGCACCAT

7681 AACACACAATCAACAGGGGAGTGAGCTGGaaatttgctagcgaattaattc 7731
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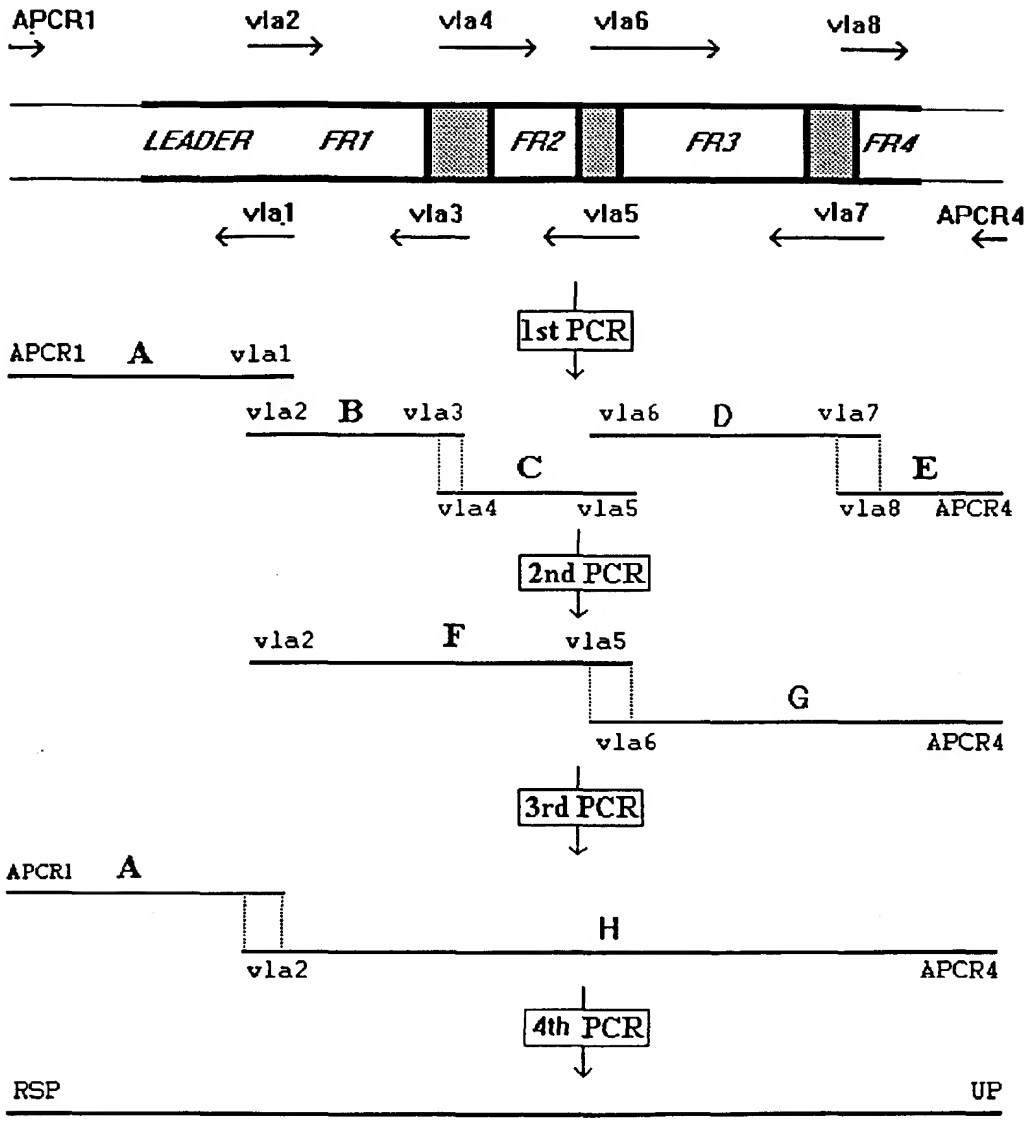
Fig. 28: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vla2 B vla3
vla6 D vla7
C
E
vla4 vla5
vla8 APCR4
2nd PCR
vla2 F vla5
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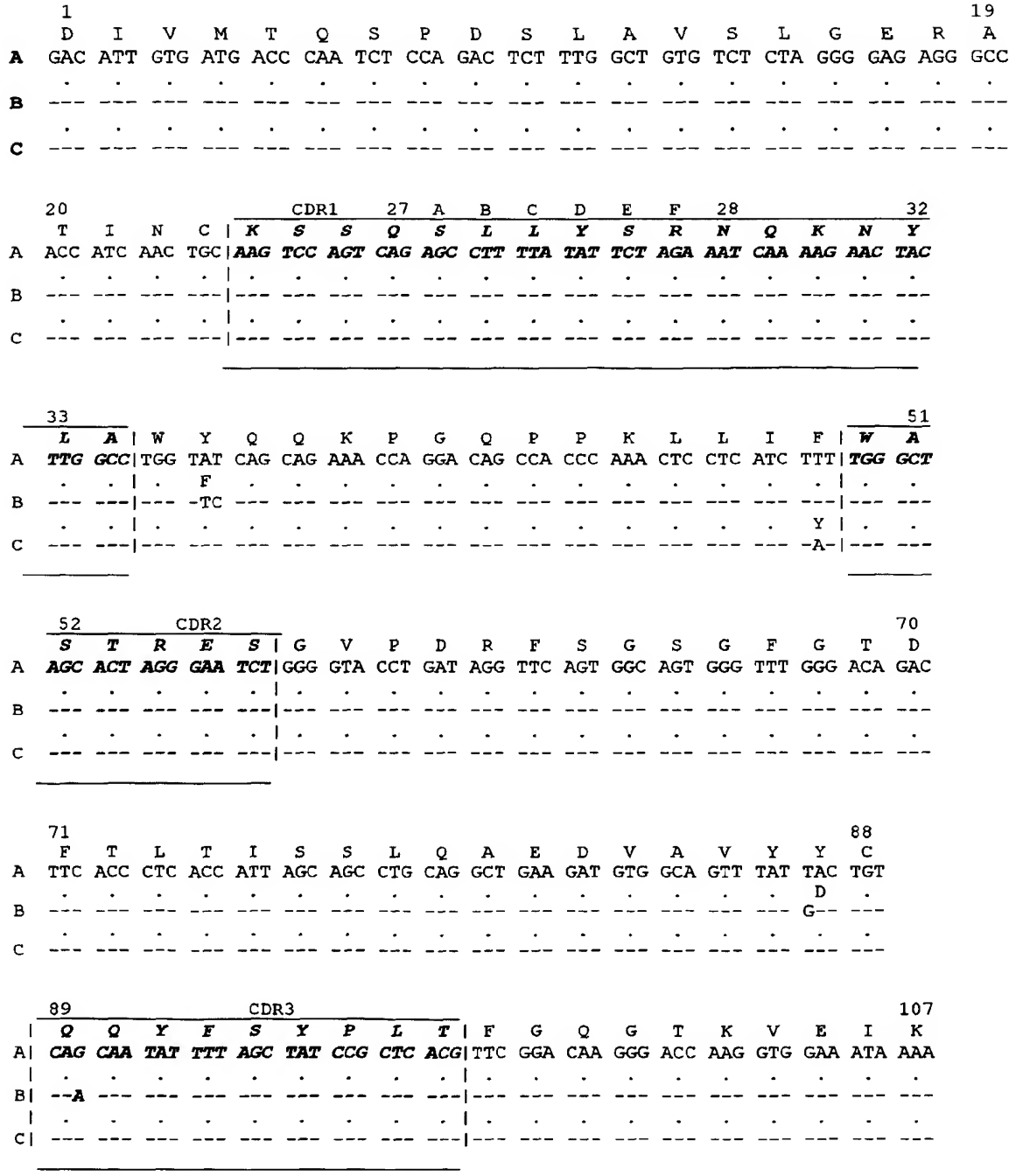
vla6
APCR4
3rd PCR
APCR1 A
H
vla2
APCR4
4th PCR
RSP
UP

Fig. 29 /1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A GAC ATT GTG ATG ACC CAA TCT CCA GAC TCT TTG GCT GTG TCT CTA GGG GAG AGG GCC
B
C
20 T I N C | CDR1 27 A B C D E F 28 32
A ACC ATC AAC TGC | K S S Q S L L Y S R N Q K N Y
AAG TCC AGT CAG AGC CTT TTA TAT TCT AGA AAT CAA AAG AAC TAC
B
C
33 L A | W Y Q Q K P G Q P P K L L I F | 51 W A
A TTG GCC | TGG TAT CAG CAG AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TTT | TGG GCT
B F -TC Y
C -A-
52 CDR2 S T R E S | G V P D R F S G S G F G T D 70
A AGC ACT AGG GAA TCT | GGG GTA CCT GAT AGG TTC AGT GGC AGT GGG TTT GGG ACA GAC
B
C
71 F T L T I S S L Q A E D V A V Y Y C 88
A TTC ACC CTC ACC ATT AGC AGC CTG CAG GCT GAA GAT GTG GCA GTT TAT TAC TGT
B D G--
C
89 CDR3 Q Q Y F S Y P L T | F G Q G T K V E I K 107
A| CAG CAA TAT TTT AGC TAT CCG CTC ACG | TTC GGA CAA GGG ACC AAG GTG GAA ATA AAA
B| --A
C|

Fig. 30 /1

Spe I

1 gaattccagc acactggcgg ccgttACTAG TTATTAATAG TAATCAATTA

51 CGGGGTCATT AGTTCATAGC CCATATATGG AGTTCCGCGT TACATAACTT

101 ACGGTAAATG GCCCGCCTGG CTGACCGCCC AACGACCCCC GCCCATTGAC

151 GTCAATAATG ACGTATGTTC CCATAGTAAC GCCAATAGGG ACTTTCCATT

201 GACGTCAATG GGTGGAGTAT TTACGGTAAA CTGCCCACTT GGCAGTACAT

251 CAAGTGTATC ATATGCCAAG TACGCCCCCT ATTGACGTCA ATGACGGTAA

301 ATGGCCCGCC TGGCATTATG CCCAGTACAT GACCTTATGG GACTTTCCTA

SnaB I

351 CTTGGCAGTA CATCTACGTA TTAGTCATCG CTATTACCAT GGTGATGCGG

401 TTTTGGCAGT ACATCAATGG GCGTGGATAG CGGTTTGACT CACGGGGATT

451 TCCAAGTCTC CACCCCATTG ACGTCAATGG GAGTTTGTTT TGGCACCAAA

501 ATCAACGGGA CTTTCCAAAA TGTCGTAACA ACTCCGCCCC ATTGACGCAA

551 ATGGGCGGTA GGCGTGTACG GTGGGAGGTC TATATAAGCA GAGCTCGTTT

601 AGTGAACCGT CAGATCGCCT GGAGACGCCA TCCACGCTGT TTTGACCTCC

Sac II

651 ATAGAAGACA CCGGGACCGA TCCAGCCTCC GCGGCCGGGA ACGGTGCATT

701 GGAACGCGGA TTCCCCGTGC CAAGAGTGAC GTAAGTACCG CCTATAGAGT

751 CTATAGGCCC ACCCCCTTGG CTTCTTATGC ATGCTATACT GTTTTTGGCT

801 TGGGGTCTAT ACACCCCCGC TTCCTCATGT TATAGGTGAT GGTATAGCTT

851 AGCCTATAGG TGTGGGTTAT TGACCATTAT TGACCACTCC CCTATTGGTG

901 ACGATACTTT CCATTACTAA TCCATAACAT GGCTCTTTGC CACAACTCTC

951 TTTATTGGCT ATATGCCAAT ACACTGTCCT TCAGAGACTG ACACGGACTC

1001 TGTATTTTTA CAGGATGGGG TCTCATTTAT TATTTACAAA TTCACATATA

1051 CAACACCACC GTCCCCAGTG CCCGCAGTTT TTATTAAACA TAACGTGGGA

(BspE I)

1101 TCTCCACGCG AATCTCGGGT ACGTGTTCCG GACATGGGCT CTTCTCCGGT

1151 AGCGGCGGAG CTTCTACATC CGAGCCCTGC TCCCATGCCT CCAGCGACTC

1201 ATGGTCGCTC GGCAGCTCCT TGCTCCTAAC AGTGGAGGCC AGACTTAGGC

Fig. 30 /2

1251 ACAGCACGAT GCCCACCACC ACCAGTGTGC CGCACAAGGC CGTGGCGGTA

1301 GGGTATGTGT CTGAAAATGA GCTCggggag cgggcttgca ccgctgacgc
AfI II
1351 atttggaaga cttaaggcag cggcagaaga agatgcaggc agctgagttg

1401 ttgtgttctg ataagagtca gaggtaactc ccgttgcggt gctgttaacg

1451 gtggagggca gtgtagtctg agcagtactc gttgctgccg cgcgcgccac

1501 cagacataat agctgacaga ctaacagact gttcctttcc atgggtcttt
Mlu I Hind III
1551 tctgcagtca ccgtccttga cacgcgtctc gggaagcttG CCGCCACCAT
M
1601 GGAGACAGAC ACACTCCTGC TATGGGTGCT GCTGCTCTGG GTTCCAGGTT
E T D T L L L W V L L L W V P G
(BspE I)
1651 CCTCCGGAGA CATTGTGATG ACCCAATCTC CAGACTCTTT GGCTGTGTCT
S S G D I V M T Q S P D S L A V S

1701 CTAGGGGAGA GGGCCACCAT CAACTGCAAG TCCAGTCAGA GCCTTTTATA
L G E R A T I N C *K S S Q S L L Y*
XbaI *CDR 1*
1751 TTCTAGAAAT CAAAAGAACT ACTTGGCCTG GTATCAGCAG AAACCAGGAC
S R N Q K N Y L A W Y Q Q K P G
KpnI
1801 AGCCACCCAA ACTCCTCATC TTTTGGGCTA GCACTAGGGA ATCTGGGGTA
Q P P K L L I F *W A S T R E S* G V
CDR 2
1851 CCTGATAGGT TCAGTGGCAG TGGGTTTGGG ACAGACTTCA CCCTCACCAT
P D R F S G S G F G T D F T L T I

1901 TAGCAGCCTG CAGGCTGAAG ATGTGGCAGT TTATTACTGT CAGCAATATT
S S L Q A E D V A V Y Y C *Q Q Y*
1951 TTAGCTATCC GCTCACGTTC GGACAAGGGA CCAAGGTGGA AATAAAACGT
F S Y P L T F G Q G T K V E I K R
CDR 3
BamH I
2001 GAGTggatcc ATCTGGGATA AGCATGCTGT TTTCTGTCTG TCCCTAACAT

2051 GCCCTGTGAT TATGCGCAAA CAACACACCC AAGGGCAGAA CTTTGTTACT

2101 TAAACACCAT CCTGTTTGCT TCTTTCCTCA GGAACTGTGG CTGCACCATC
T V A A P S
2151 TGTCTTCATC TTCCCGCCAT CTGATGAGCA GTTGAAATCT GGAACTGCCT
V F I F P P S D E Q L K S G T A
2201 CTGTTGTGTG CCTGCTGAAT AACTTCTATC CCAGAGAGGC CAAAGTACAG
S V V C L L N N F Y P R E A K V Q
2251 TGGAAGGTGG ATAACGCCCT CCAATCGGGT AACTCCCAGG AGAGTGTCAC
W K V D N A L Q S G N S Q E S V T
2301 AGAGCAGGAC AGCAAGGACA GCACCTACAG CCTCAGCAGC ACCCTGACGC

Fig. 30 /3

```
        E Q D S K D S T Y S L S S T L T
2351 TGAGCAAAGC AGACTACGAG AAACACAAAG TCTACGCCTG CGAAGTCACC
     L S K A D Y E K H K V Y A C E V T
2401 CATCAGGGCC TGAGCTCGCC CGTCACAAAG AGCTTCAACA GGGGAGAGTG
       H Q G L S S P V T K S F N R G E C
2451 TTAGAGGGAG AAGTGCCCCC ACCTGCTCCT CAGTTCCAGC CTGACCCCCT
       *                                          Psp5 II
2501 CCCATCCTTT GGCCTCTGAC CCTTTTTCCA CAGGGGACCT ACCCCTATTG

2551 CGGTCCTCCA GCTCATCTTT CACCTCACCC CCCTCCTCCT CCTTGGCTTT

2601 AATTATGCTA ATGTTGGAGG AGAATGAATA AATAAAGTGA ATCTTTGCAC

2651 CTGTGGTGGA TCTAATAAAA GATATTTATT TTCATTAGAT ATGTGTGTTG

2701 GTTTTTTGTG TGCAGTGCCT CTATCTGGAG GCCAGGTAGG GCTGGCCTTG

2751 GGGGAGGGGG AGGCCAGAAT GACTCCAAGA GCTACAGGAA GGCAGGTCAG

2801 AGACCCCACT GGACAAACAG TGGCTGGACT CTGCACCATA ACACACAATC

2851 AACAGGGGAG TGAGCTGGAA ATTTGCTAGC GAATTCTTGA AGACGAAAGG

2901 GCCTCGTGAT ACGCCTATTT TTATAGGTTA ATGTCATGAT AATAATGGTT

2951 TCTTAGACGT CAGGTGGCAC TTTTCGGGGA AATGTGCGCG GAACCCCTAT

3001 TTGTTTATTT TTCTAAATAC ATTCAAATAT GTATCCGCTC ATGAGACAAT

3051 AACCCTGATA AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT

3101 CAACATTTCC GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC

3151 TGTTTTTGCT CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAAGATC

3201 AGTTGGGTGC ACGAGTGGGT TACATCGAAC TGGATCTCAA CAGCGGTAAG

3251 ATCCTTGAGA GTTTTCGCCC CGAAGAACGT TTTCCAATGA TGAGCACTTT

3301 TAAAGTTCTG CTATGTGGCG CGGTATTATC CCGTGTTGAC GCCGGGCAAG

3351 AGCAACTCGG TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC

3401 TCACCAGTCA CAGAAAAGCA TCTTACGGAT GGCATGACAG TAAGAGAATT

3451 ATGCAGTGCT GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC
                Pvu I
3501 TGACAACGAT CGGAGGACCG AAGGAGCTAA CCGCTTTTTT GCACAACATG

3551 GGGGATCATG TAACTCGCCT TGATCGTTGG GAACCGGAGC TGAATGAAGC
```

Fig. 30 /4

3601 CATACCAAAC GACGAGCGTG ACACCACGAT GCCTGCAGCA ATGGCAACAA

3651 CGTTGCGCAA ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA

3701 CAATTAATAG ACTGGATGGA GGCGGATAAA GTTGCAGGAC CACTTCTGCG

3751 CTCGGCCCTT CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG

3801 AGCGTGGGTC TCGCGGTATC ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC

3851 TCCCGTATCG TAGTTATCTA CACGACGGGG AGTCAGGCAA CTATGGATGA

3901 ACGAAATAGA CAGATCGCTG AGATAGGTGC CTCACTGATT AAGCATTGGT

3951 AACTGTCAGA CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT

4001 CATTTTTAAT TTAAAAGGAT CTAGGTGAAG ATCCTTTTTG ATAATCTCAT

4051 GACCAAAATC CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG

4101 TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT GCGCGTAATC

4151 TGCTGCTTGC AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC

4201 GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG

4251 CGCAGATACC AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC

4301 TTCAAGAACT CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT

4351 ACCAGTGGCT GCTGCCAGTG GCGATAAGTC GTGTCTTACC GGGTTGGACT

4401 CAAGACGATA GTTACCGGAT AAGGCGCAGC GGTCGGGCTG AACGGGGGGT

4451 TCGTGCACAC AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA

4501 CCTACAGCGT GAGCTATGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG

4551 CGGACAGGTA TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG

4601 GAGCTTCCAG GGGGAAACGC CTGGTATCTT TATAGTCCTG TCGGGTTTCG

4651 CCACCTCTGA CTTGAGCGTC GATTTTTGTG ATGCTCGTCA GGGGGGCGGA

4701 GCCTATGGAA AAACGCCAGC AACGCGGCCT TTTTACGGTT CCTGGCCTTT

BspLU11I

4751 TGCTGGCCTT TTGCTC**ACAT GT**TCTTTCCT GCGTTATCCC CTGATTCTGT

4801 GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT CGCCGCAGCC

Fig. 30 /5

4851 GAACGACCGA GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCCTG

4901 ATGCGGTATT TTCTCCTTAC GCATCTGTGC GGTATTTCAC ACCGCATATG

Bst1107I

4951 GTGCACTCTC AGTACAATCT GCTCTGATGC CGCATAGTTA AGCCA**GTATA**

5001 CACTCCGCTA TCGCTACGTG ACTGGGTCAT GGCTGCGCCC CGACACCCGC

5051 CAACACCCGC TGACGCGCCC TGACGGGCTT GTCTGCTCCC GGCATCCGCT

5101 TACAGACAAG CTGTGACCGT CTCCGGGAGC TGCATGTGTC AGAGGTTTTC

5151 ACCGTCATCA CCGAAACGCG CGAGGCAGCT GTGGAATGTG TGTCAGTTAG

5201 GGTGTGGAAA GTCCCCAGGC TCCCCAGCAG GCAGAAGTAT GCAAAGCATG

5251 CATCTCAATT AGTCAGCAAC CAGGCTCCCC AGCAGGCAGA AGTATGCAAA

5301 GCATGCATCT CAATTAGTCA GCAACCATAG TCCCGCCCCT AACTCCGCCC

5351 ATCCCGCCCC TAACTCCGCC CAGTTCCGCC CATTCTCCGC CCCATGGCTG

Sfi I

5401 ACTAATTTTT TTTATTTATG CAGAGGCCGA **GGCCGCCTCG GCC**TCTGAGC

Stu I/Avr II

5451 TATTCCAGAA GTAGTGAGGA GGCTTTTTTG G**AGGCCTAGG** CTTTTGCAAA

5501 AAGCTAGCTT CACGCTGCCG CAAGCACTCA GGGCGCAAGG GCTGCTAAAG

5551 GAAGCGGAAC ACGTAGAAAG CCAGTCCGCA GAAACGGTGC TGACCCCGGA

5601 TGAATGTCAG CTACTGGGCT ATCTGGACAA GGGAAAACGC AAGCGCAAAG

5651 AGAAAGCAGG TAGCTTGCAG TGGGCTTACA TGGCGATAGC TAGACTGGGC

5701 GGTTTTATGG ACAGCAAGCG AACCGGAATT GCCAGCTGGG GCGCCCTCTG

5751 GTAAGGTTGG GAAGCCCTGC AAAGTAAACT GGATGGCTTT CTTGCCGCCA

Bgl II/Bcl I

5801 AGGATCTGAT GGCGCAGGGG ATCA**AGATCT GATCA**AGAGA CAGGATGAGG

5851 ATCGTTTCGC ATGATTGAAC AAGATGGATT GCACGCAGGT TCTCCGGCCG

5901 CTTGGGTGGA GAGGCTATTC GGCTATGACT GGGCACAACA GACAATCGGC

5951 TGCTCTGATG CCGCCGTGTT CCGGCTGTCA GCGCAGGGGC GCCCGGTTCT

6001 TTTTGTCAAG ACCGACCTGT CCGGTGCCCT GAATGAACTG CAGGACGAGG

Msc I

6051 CAGCGCGGCT ATCGTGGC**TG GCCA**CGACGG GCGTTCCTTG CGCAGCTGTG

Fig. 30 /6

6101 CTCGACGTTG TCACTGAAGC GGGAAGGGAC TGGCTGCTAT TGGGCGAAGT

6151 GCCGGGGCAG GATCTCCTGT CATCTCACCT TGCTCCTGCC GAGAAAGTAT

6201 CCATCATGGC TGATGCAATG CGGCGGCTGC ATACGCTTGA TCCGGCTACC

6251 TGCCCATTCG ACCACCAAGC GAAACATCGC ATCGAGCGAG CACGTACTCG

6301 GATGGAAGCC GGTCTTGTCG ATCAGGATGA TCTGGACGAA GAGCATCAGG

6351 GGCTCGCGCC AGCCGAACTG TTCGCCAGGC TCAAGGCGCG CATGCCCGAC

6401 GGCGAGGATC TCGTCGTGAC CCATGGCGAT GCCTGCTTGC CGAATATCAT

6451 GGTGGAAAAT GGCCGCTTTT CTGGATTCAT CGACTGTGGC CGGCTGGGTG

Rsr II

6501 TGG**CGGACCG** CTATCAGGAC ATAGCGTTGG CTACCCGTGA TATTGCTGAA

6551 GAGCTTGGCG GCGAATGGGC TGACCGCTTC CTCGTGCTTT ACGGTATCGC

6601 CGCTCCCGAT TCGCAGCGCA TCGCCTTCTA TCGCCTTCTT GACGAGTTCT

Nsp V

6651 TCTGAGCGGG ACTCTGGGG**T TCGAA**ATGAC CGACCAAGCG ACGCCCAACC

6701 TGCCATCACG AGATTTCGAT TCCACCGCCG CCTTCTATGA AAGGTTGGGC

6751 TTCGGAATCG TTTTCCGGGA CGCCGGCTGG ATGATCCTCC AGCGCGGGGA

Sma I Nru I

6801 TCTCATGCTG GAGTTCTTCG CCCAC**CCCGG G**CTCGATCCC C**TCGCGA**GTT

6851 GGTTCAGCTG CTGCCTGAGG CTGGACGACC TCGCGGAGTT CTACCGGCAG

6901 TGCAAATCCG TCGGCATCCA GGAAACCAGC AGCGGCTATC CGCGCATCCA

6951 TGCCCCCGAA CTGCAGGAGT GGGGAGGCAC GATGGCCGCT TTGGTCCCGG

7001 ATCTTTGTGA AGGAACCTTA CTTCTGTGGT GTGACATAAT TGGACAAACT

7051 ACCTACAGAG ATTTAAAGCT CTAAGGTAAA TATAAAATTT TTAAGTGTAT

7101 AATGTGTTAA ACTACTGATT CTAATTGTTT GTGTATTTTA GATTCCAACC

7151 TATGGAACTG ATGAATGGGA GCAGTGGTGG AATGCCTTTA ATGAGGAAAA

7201 CCTGTTTTTGC TCAGAAGAAA TGCCATCTAG TGATGATGAG GCTACTGCTG

7251 ACTCTCAACA TTCTACTCCT CCAAAAAAGA AGAGAAAGGT AGAAGACCCC

7301 AAGGACTTTC CTTCAGAATT GCTAAGTTTT TTGAGTCATG CTGTGTTTAG

Fig. 30 /7

7351 TAATAGAACT CTTGCTTGCT TTGCTATTTA CACCACAAAG GAAAAAGCTG

7401 CACTGCTATA CAAGAAAATT ATGGAAAAAT ATTCTGTAAC CTTTATAAGT

7451 AGGCATAACA GTTATAATCA TAACATACTG TTTTTTCTTA CTCCACACAG

7501 GCATAGAGTG TCTGCTATTA ATAACTATGC TCAAAAATTG TGTACCTTTA

7551 GCTTTTTAAT TTGTAAAGGG GTTAATAAGG AATATTTGAT GTATAGTGCC

7601 TTGACTAGAG ATCATAATCA GCCATACCAC ATTTGTAGAG GTTTTACTTG

7651 CTTTAAAAAA CCTCCCACAC CTCCCCCTGA ACCTGAAACA TAAAATGAAT

Mun I

7701 G**CAATTG**TTG TTGTTAACTT GTTTATTGCA GCTTATAATG GTTACAAATA

7751 AAGCAATAGC ATCACAAATT TCACAAATAA AGCATTTTTT TCACTGCATT

7801 CTAGTTGTGG TTTGTCCAAA CTCATCAATG TATCTTATCA TGTCTGGATC

7851 TAATAAAAGA TATTTATTTT CATTAGATAT GTGTGTTGGT TTTTTGTGTG

7901 CAGTGCCTCT ATCTGGAGGC CAGGTAGGGC TGGCCTTGGG GGAGGGGGAG

7951 GCCAGAATGA CTCCAAGAGC TACAGGAAGG CAGGTCAGAG ACCCCACTGG

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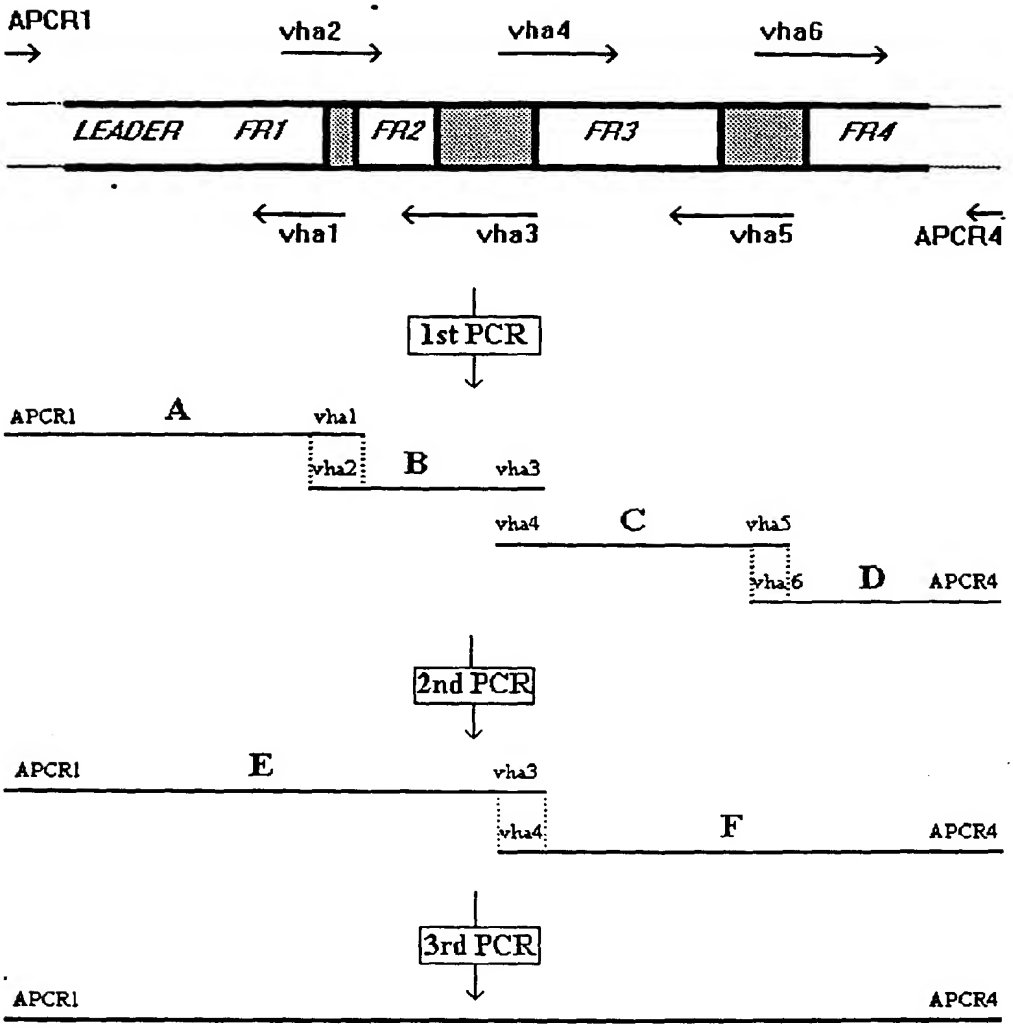
8051 AGCTGGAAAT TTGCTAGC

Fig. 31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vha6
LEADER
FR1
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FR3
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A
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C
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3rd PCR
APCR1
APCR4

Fig. 32 /1

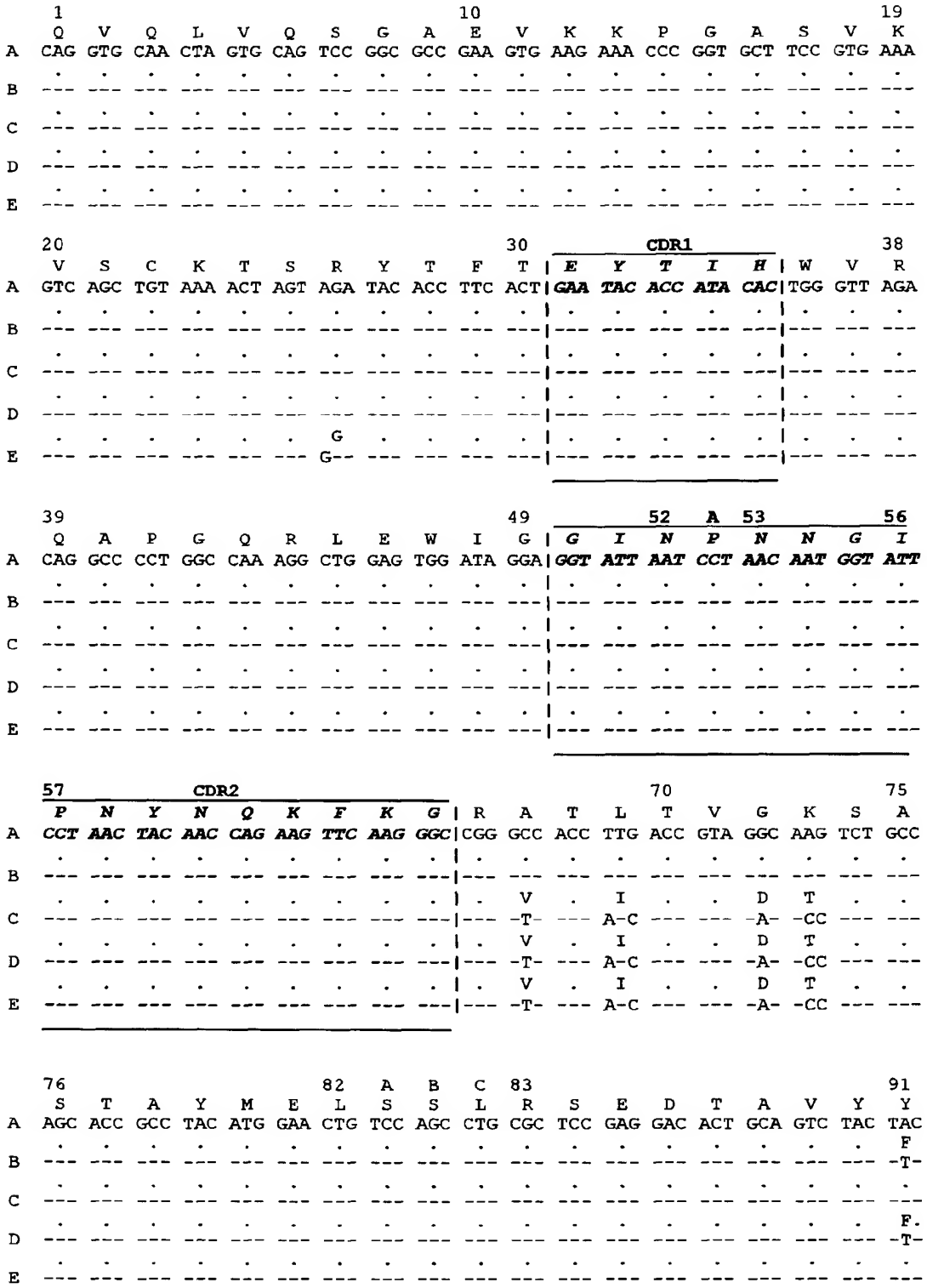


Fig. 32 /2

	92			CDR3					100	A	B	C	D	I	J	K	101		103
	C	A	R	R	R	I	A	Y	G	Y	D	E	G	H	A	M	D	Y	W
A	TGC	GCC	AGA	AGA	AGA	ATC	GCC	TAT	GGT	TAC	GAC	GAG	GGC	CAT	GCT	ATG	GAC	TAC	TGG
B	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

	104									113
	G	Q	G	T	L	V	T	V	S	S
A	GGT	CAA	GGA	ACC	CTT	GTC	ACC	GTC	TCC	TCA
B	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---
C	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---
D	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---
E	.	.	.	.	.	.	.	.	.	.
	---	---	---	---	---	---	---	---	---	---

Fig. 33 /1

```
   1 TTGAAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAAT

  61 GGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTT

 121 ATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCT

 181 TCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCC

 241 CTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAA

 301 AGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGG

 361 TAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGT

 421 TCTGCTATGTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCG

 481 CATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTAC

 541 GGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGC

                          Pvu I
 601 GGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAA

 661 CATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACC

                                                  Fsp I
 721 AAACGACGAGCGTGACACCACGATGCCTGCAGCAATGGCAACAACGTTGCGCAAACTATT

 781 AACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGA
```

Fig. 33 /2

```
 841 TAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAA

 901 ATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAA

961 GCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAA

1021 TAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGT

1081 TTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGT

1141 GAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTG

1201 AGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGT

1261 AATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCA

1321 AGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATAC

1381 TGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTAC

1441 ATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCT

1501 TACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGG

1561 GGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACA

1621 GCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGT

1681 AAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTA

1741 TCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTC

1801 GTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGC
                          BspLU11I
1861 CTTTTGCTGGCCTTTTGCTC**ACATGT**TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAA

1921 CCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAG

1981 CGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCTGATGCGGTATTTTCTCCTTACGCATCT

2041 GTGCGGTATTTCACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATA
            Bst1107 I
2101 GTTAAGCCA**GTATAC**ACTCCGCTATCGCTACGTGACTGGGTCATGGCTGCGCCCCGACAC

2161 CCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGA

2221 CAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAA

2281 CGCGCGAGGCAGCATGCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCC

2341 CATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTT
                                  Sfi I
2401 TTTTATTTATGCAGAGGCCGA**GGCC**GCCTC**GGCC**TCTGAGCTATTCCAGAAGTAGTGAGG
                Stu I/Avr II
2461 AGGCTTTTTTGG**AGGCCTAGG**CTTTTGCAAAAAGCTAGCTTACAGCTCAGGGCTGCGATT
```

Fig. 33 /2

2521 TCGCGCCAAACTTGACGGCAATCCTAGCGTGAAGGCTGGTAGGATTTTATCCCCGCTGCC

2581 ATCATGGTTCGACCATTGAACTGCATCGTCGCCGTGTCCCAAAATATGGGGATTGGCAAG

2641 AACGGAGACCTACCCTGGCCTCCGCTCAGGAACGAGTTCAAGTACTTCCAAAGAATGACC

2701 ACAACCTCTTCAGTGGAAGGTAAACAGAATCTGGTGATTATGGGTAGGAAAACCTGGTTC

2761 TCCATTCCTGAGAAGAATCGACCTTTAAAGGACAGAATTAATATAGTTCTCAGTAGAGAA

2821 CTCAAAGAACCACCACGAGGAGCTCATTTTCTTGCCAAAAGTTTGGATGATGCCTTAAGA

2881 CTTATTGAACAACCGGAATTGGCAAGTAAAGTAGACATGGTTTGGATAGTCGGAGGCAGT

2941 TCTGTTTACCAGGAAGCCATGAATCAACCAGGCCACCTCAGACTCTTTGTGACAAGGATC

3001 ATGCAGGAATTTGAAAGTGACACGTTTTTCCCAGAAATTGATTTGGGGAAATATAAACTT

3061 CTCCCAGAATACCCAGGCGTCCTCTCTGAGGTCCAGGAGGAAAAAGGCATCAAGTATAAG

3121 TTTGAAGTCTACGAGAAGAAAGACTAACAGGAAGATGCTTTCAAGTTCTCTGCTCCCCTC

Bgl II

3181 CTAAAGCTATGCATTTTTATAAGACCATGGGACTTTTGCTGGCTTT**AGATCT**TTGTGAAG

3241 GAACCTTACTTCTGTGGTGTGACATAATTGGACAAACTACCTACAGAGATTTAAAGCTCT

3301 AAGGTAAATATAAAATTTTTAAGTGTATAATGTGTTAAACTACTGATTCTAATTGTTTGT

3361 GTATTTTAGATTCCAACCTATGGAACTGATGAATGGGAGCAGTGGTGGAATGCCTTTAAT

3421 GAGGAAAACCTGTTTTGCTCAGAAGAAATGCCATCTAGTGATGATGAGGCTACTGCTGAC

3481 TCTCAACATTCTACTCCTCCAAAAAAGAAGAGAAAGGTAGAAGACCCCAAGGACTTTCCT

3541 TCAGAATTGCTAAGTTTTTTGAGTCATGCTGTGTTTAGTAATAGAACTCTTGCTTGCTTT

3601 GCTATTTACACCACAAAGGAAAAAGCTGCACTGCTATACAAGAAAATTATGGAAAAATAT

3661 TCTGTAACCTTTATAAGTAGGCATAACAGTTATAATCATAACATACTGTTTTTTCTTACT

3721 CCACACAGGCATAGAGTGTCTGCTATTAATAACTATGCTCAAAAATTGTGTACCTTTAGC

3781 TTTTTAATTTGTAAAGGGGTTAATAAGGAATATTTGATGTATAGTGCCTTGACTAGA**GAT**

BsaB I

3841 **CATA**ATCAGCCATACCACATTTGTAGAGGTTTTACTTGCTTTAAAAAACCTCCCACACCT

Mun I

3901 CCCCCTGAACCTGAAACATAAAATGAATG**CAATTG**TTGTTGTTAACTTGTTTATTGCAGC

3961 TTATAATGGTTACAAATAAAGCAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTC

4021 ACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGGATCTA

4081 ATAAAAGATATTTATTTTCATTAGATATGTGTGTTGGTTTTTTGTGTGCAGTGCCTCTAT

4141 CTGGAGGCCAGGTAGGGCTGGCCTTGGGGGAGGGGGAGGCCAGAATGACTCCAAGAGCTA

Fig. 33 /3

```
4201 CAGGAAGGCAGGTCAGAGACCCCACTGGACAAACAGTGGCTGGACTCTGCACCATAACAC
                                                EcoR I
4261 ACAATCAACAGGGGAGTGAGCTGGAAATTTGCTAGCGAATTCcagcacactggcggccgt
      (Spe I)
4321 tACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTT

4381 CCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCC

4441 ATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACG

4501 TCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATAT

4561 GCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCA
                                                SnaB I
4621 GTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTAT

4681 TACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACG

4741 GGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCA

4801 ACGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCG

4861 TGTACGGTGGGAGGTCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG

4921 ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGG

4981 CCGGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTA

5041 TAGAGTCTATAGGCCCACCCCCTTGGCTTCTTATGCATGCTATACTGTTTTTGGCTTGGG
                                                Bpu1102I
5101 GTCTATACACCCCCGCTTCCTCATGTTATAGGTGATGGTATAGCTTAGCCTATAGGTGTG
                                Xcm I
5161 GGTTATTGACCATTATTGACCACTCCCCTATTGGTGACGATACTTTCCATTACTAATCCA

5221 TAACATGGCTCTTTGCCACAACTCTCTTTATTGGCTATATGCCAATACACTGTCCTTCAG

5281 AGACTGACACGGACTCTGTATTTTTACAGGATGGGGTCTCATTTATTATTTACAAATTCA

5341 CATATACAACACCACCGTCCCCAGTGCCCGCAGTTTTTATTAAACATAACGTGGGATCTC
                                BspE I
5401 CACGCGAATCTCGGGTACGTGTTCCGGACATGGGCTCTTCTCCGGTAGCGGCGGAGCTTC

5461 TACATCCGAGCCCTGCTCCCATGCCTCCAGCGACTCATGGTCGCTCGGCAGCTCCTTGCT

5521 CCTAACAGTGGAGGCCAGACTTAGGCACAGCACGATGCCCACCACCACCAGTGTGCCGCA

5581 CAAGGCCGTGGCGGTAGGGTATGTGTCTGAAAATGAGCTCggggagcgggcttgcaccgc
                                                (Pvu II)
5641 tgacgcatttggaagacttaaggcagcggcagaagaagatgcaggcagctgagttgttgt

5701 gttctgataagagtcagaggtaactcccgttgcggtgctgttaacggtggagggcagtgt

5761 agtctgagcagtactcgttgctgccgcgcgcgccaccagacataatagctgacagactaa
                                                Mlu I
5821 cagactgttcctttccatgggtcttttctgcagtcaccgtccttgacACGCGTCTCGGGA
```

Fig. 33 /4

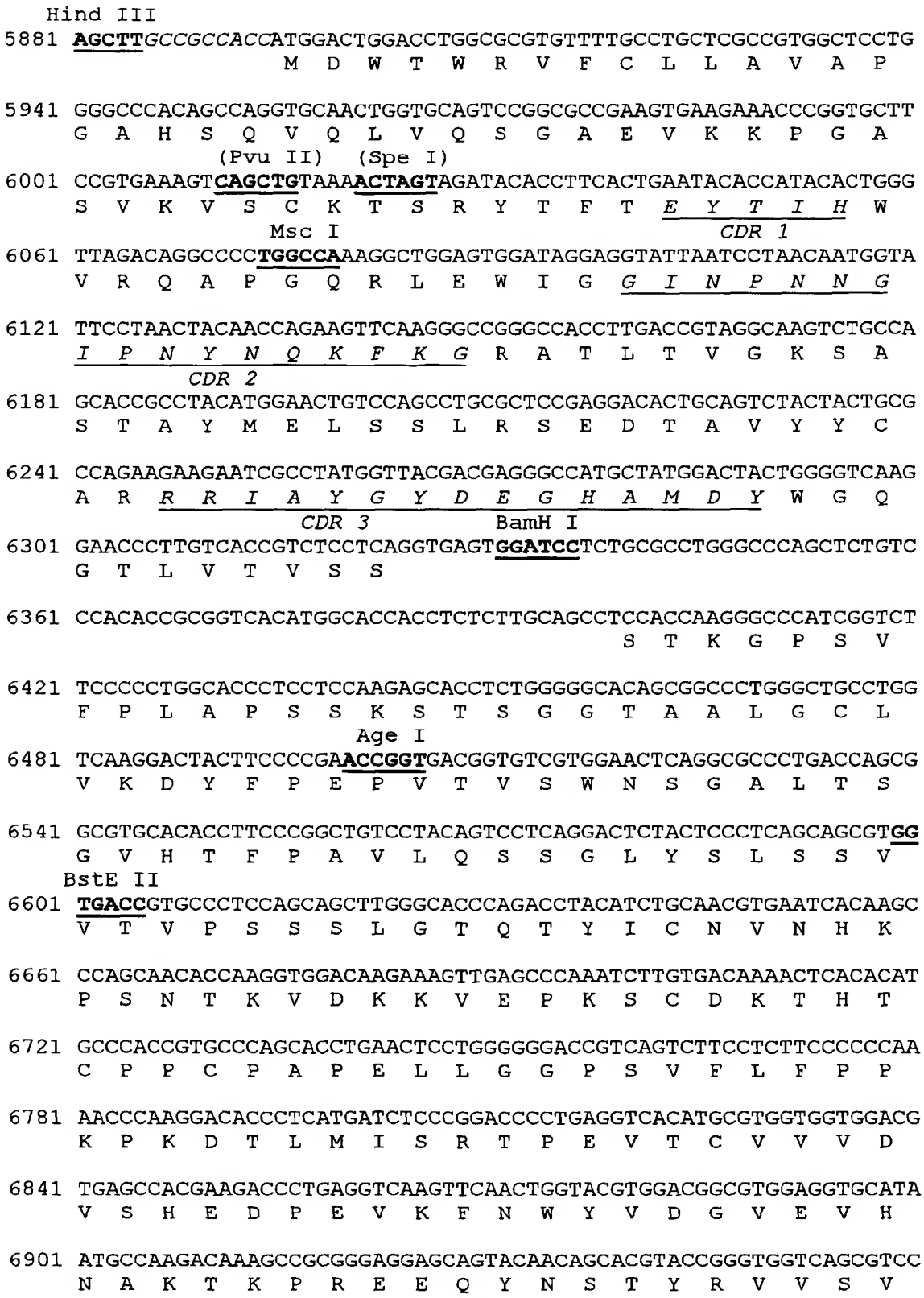

Hind III
5881 AGCTTGCCGCCACCATGGACTGGACCTGGCGCGTGTTTTGCCTGCTCGCCGTGGCTCCTG
M D W T W R V F C L L A V A P
5941 GGGCCCACAGCCAGGTGCAACTGGTGCAGTCCGGCGCCGAAGTGAAGAAACCCGGTGCTT
G A H S Q V Q L V Q S G A E V K K P G A
(Pvu II) (Spe I)
6001 CCGTGAAAGTCAGCTGTAAAACTAGTAGATACACCTTCACTGAATACACCATACACTGGG
S V K V S C K T S R Y T F T E Y T I H W
Msc I
CDR 1
6061 TTAGACAGGCCCCTGGCCAAAGGCTGGAGTGGATAGGAGGTATTAATCCTAACAATGGTA
V R Q A P G Q R L E W I G G I N P N N G
6121 TTCCTAACTACAACCAGAAGTTCAAGGGCCGGGCCACCTTGACCGTAGGCAAGTCTGCCA
I P N Y N Q K F K G R A T L T V G K S A
CDR 2
6181 GCACCGCCTACATGGAACTGTCCAGCCTGCGCTCCGAGGACACTGCAGTCTACTACTGCG
S T A Y M E L S S L R S E D T A V Y Y C
6241 CCAGAAGAAGAATCGCCTATGGTTACGACGAGGGCCATGCTATGGACTACTGGGGTCAAG
A R R R I A Y G Y D E G H A M D Y W G Q
CDR 3
BamH I
6301 GAACCCTTGTCACCGTCTCCTCAGGTGAGTGGATCCTCTGCGCCTGGGCCCAGCTCTGTC
G T L V T V S S
6361 CCACACCGCGGTCACATGGCACCACCTCTCTTGCAGCCTCCACCAAGGGCCCATCGGTCT
S T K G P S V
6421 TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGG
F P L A P S S K S T S G G T A A L G C L
Age I
6481 TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCG
V K D Y F P E P V T V S W N S G A L T S
6541 GCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG
G V H T F P A V L Q S S G L Y S L S S V
BstE II
6601 TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGC
V T V P S S S L G T Q T Y I C N V N H K
6661 CCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACAT
P S N T K V D K K V E P K S C D K T H T
6721 GCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAA
C P P C P A P E L L G G P S V F L F P P
6781 AACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACG
K P K D T L M I S R T P E V T C V V V D
6841 TGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA
V S H E D P E V K F N W Y V D G V E V H
6901 ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCC
N A K T K P R E E Q Y N S T Y R V V S V

Fig. 33 /5

```
6961 TCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
     L  T  V  L  H  Q  D  W  L  N  G  K  E  Y  K  C  K  V  S  N

7021 AAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
     K  A  L  P  A  P  I  E  K  T  I  S  K  A  K  G  Q  P  R  E

7081 CACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGA
     P  Q  V  Y  T  L  P  P  S  R  E  E  M  T  K  N  Q  V  S  L

7141 CCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
     T  C  L  V  K  G  F  Y  P  S  D  I  A  V  E  W  E  S  N  G

7201 AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
     Q  P  E  N  N  Y  K  T  T  P  P  V  L  D  S  D  G  S  F  F


7261 TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
     L  Y  S  K  L  T  V  D  K  S  R  W  Q  Q  G  N  V  F  S  C

7321 CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
     S  V  M  H  E  A  L  H  N  H  Y  T  Q  K  S  L  S  L  S  P
                      NgoM I
7381 GTAAATGAGTGCGACGGCCGGCAAGCCCCGCTCCCCGGGCTCTCGCGGTCGCACGAGGAT
     G  K  *
7441 GCTTGGCACGTACCCCCTGTACATACTTCCCGGGCGCCCAGCATGGAAATAAAGCACCGG

7501 ATCTAATAAAAGATATTTATTTTCATTAGATATGTGTGTTGGTTTTTTGTGTGCAGTGCC

7561 TCTATCTGGAGGCCAGGTAGGGCTGGCCTTGGGGGAGGGGGAGGCCAGAATGACTCCAAG

7621 AGCTACAGGAAGGCAGGTCAGAGACCCCACTGGACAAACAGTGGCTGGACTCTGCACCAT

7681 AACACACAATCAACAGGGGAGTGAGCTGGaaatttgctagcgaattaattc 7731
```

Fig. 34 A

INTRON

3' end V gene ---------- 5' end of CH1

ACC GTC TCC T*CA G::GTGAGT*GGATCC-(N)$_{48}$-*CCTCTCTTGCAG::C*C-

T V S S *splice donor site* BamHI *splice acceptor site*

-TCC ACC AAG GGC

S T K G ⇓

ACC GTC TCC T*CA G::::C*C TCC ACC AAG GGC

T V S S S T K G

⇓

ACC GTC TCC TCA **GCC** TCC ACC AAG GGC

T V S S **A** S T K G

Fig. 34 B

INTRON

3' end V gene ---------- 5' end Kappa constant

GAA ATA AA*A C::GTGAGT*GGATCC-$(N)_{108}$-*CTTCTTTCCTCAG::G*A-

E I K ***splice donor site***BamHI ***splice acceptor site***

-ACT GTG GCT GCA

T V A A

⇓

GAA ATA AA*A C::::G*A ACT GTG GCT GCA

E I K T V A A

⇓

GAA ATA AAA **CGA** ACT GTG GCT GCA

E I K **R** T V A A

Fig. 35

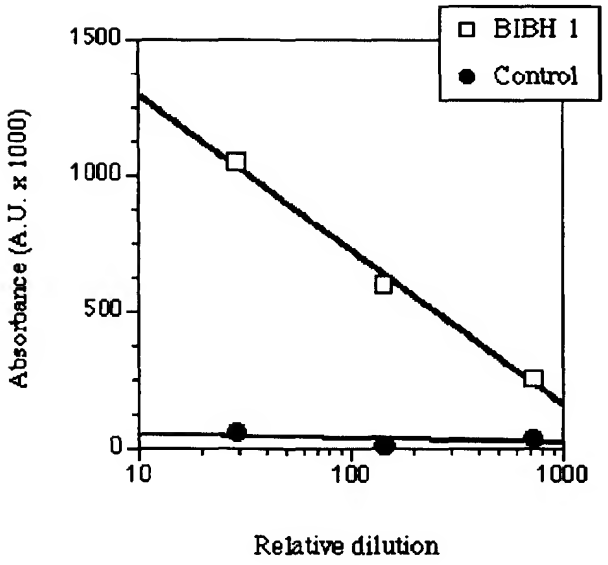


Fig. 36

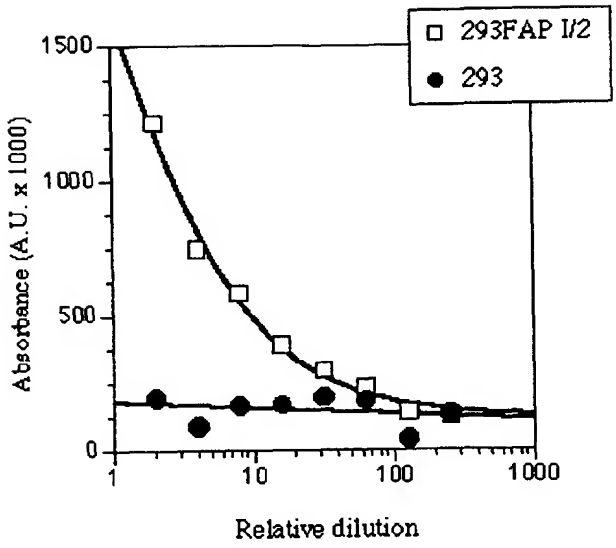
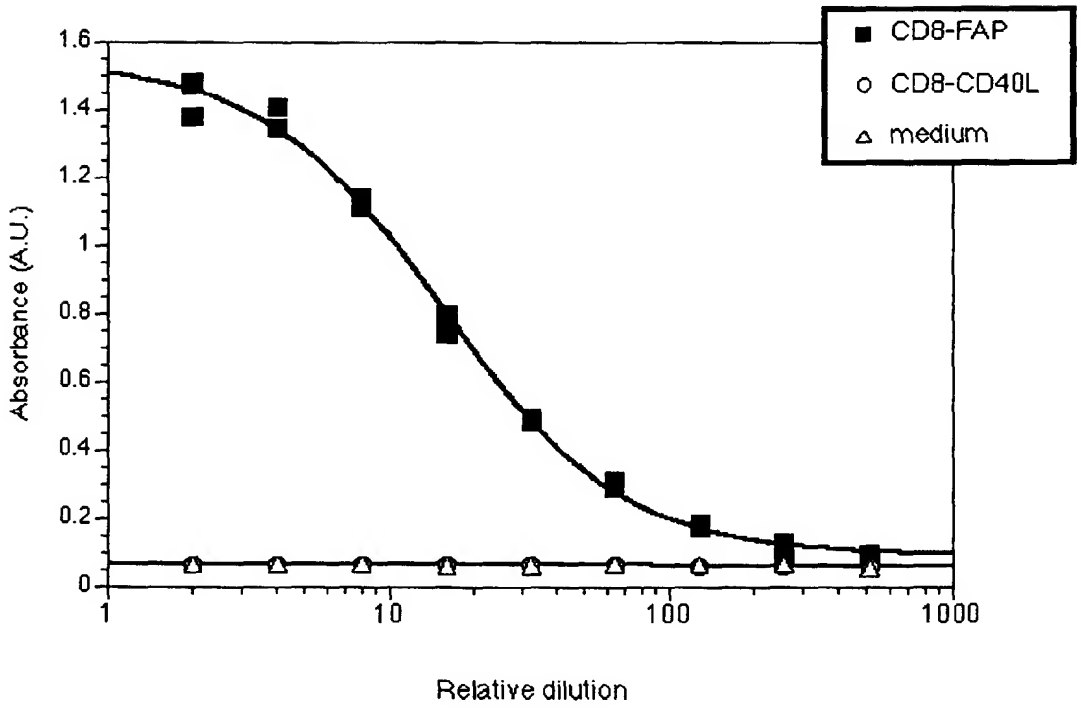

293FAP I/2
293
1500
1000
500
0
Absorbance (A.U. x 1000)
1
10
100
1000
Relative dilution

Fig. 37


CD8-FAP
CD8-CD40L
medium
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Absorbance (A.U.)
1
10
100
1000
Relative dilution

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 98 10 7925

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	WELT ET AL.: "Antibody targeting in metastatic colon cancer: a phase I study of monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal fibroblasts" JOURNAL OF CLINICAL ONCOLOGY, vol. 12, no. 6, June 1994, pages 1193-1203, XP002088696 * abstract * * page 1193, column 1, line 1 - page 1194, column 2, line 4 * * page 1202, column 2, paragraph 2 * ---	1-65	C12N15/13 C07K16/40 C07K16/46 C12N15/62 C12N15/85 C12N5/10 C07K19/00 A61K47/48 A61K51/10 A61K39/395 G01N33/577 G01N33/574
Y	WO 93 05804 A (SLOAN KETTERING INST CANCER) 1 April 1993 * abstract; claims 1-23 * ---	1-65	
Y	US 5 693 761 A (SCHNEIDER WILLIAM P ET AL) 2 December 1997 * abstract * * examples 3-9 * * column 2, line 36 - column 3, line 59 * --- -/--	1-65	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	21 December 1998	Muller-Thomalla, K

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 98 10 7925

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	STUDNICKA G M ET AL: "Human-engineered monoclonal antibodies retain full specific binding activity by preserving non- CDR complementarity-modulating residues." PROTEIN ENGINEERING, (1994 JUN) 7 (6) 805-14. JOURNAL CODE: PR1. ISSN: 0269-2139., XP000447301 ENGLAND: United Kingdom * page 805, column 1, line 1 - page 806, column 2, paragraph 1 * * page 808, column 2, paragraph 2 - page 812, column 1, paragraph 1 * * page 813, column 2, paragraph 1 * ---	1-65	
Y	WRIGHT A ET AL: "Genetically engineered antibodies: progress and prospects." CRITICAL REVIEWS IN IMMUNOLOGY, (1992) 12 (3-4) 125-68. REF: 252 JOURNAL CODE: AF1. ISSN: 1040-8401., XP000616488 United States * page 139, column 2, paragraph 3 - page 141, column 1, paragraph 3 * * page 157, column 2, paragraph 3 - page 158, column 1, paragraph 1 * ---	1-65	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	WO 94 05690 A (SMITHKLINE BEECHAM CORP ;US ARMY (US); GROSS MITCHELL STUART (US);) 17 March 1994 * claim 5; figure 3 * -----	14-17	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 98 10 7925

Although claims 50-52,54,55,57,61,62,65 are directed to a method of treatment of the human/animal body and/or a diagnostic method practised on the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.